

Substituted pyridine compounds and methods of use**Patent number:** JP2001522834T**Publication date:** 2001-11-20**Inventor:****Applicant:****Classification:**

- international: **C07D213/73; C07D213/75; C07D213/82; C07D401/12; C07D405/12; C07D409/12; C07D413/12; C07D417/12; C07D471/04; C07D213/00; C07D401/00; C07D405/00; C07D409/00; C07D413/00; C07D417/00; C07D471/00; (IPC1-7): C07D213/75; A61K31/44; A61K31/443; A61K31/4436; A61K31/4439; A61K31/444; A61K31/496; A61P1/04; A61P3/10; A61P3/14; A61P9/02; A61P9/10; A61P11/00; A61P11/06; A61P17/00; A61P17/06; A61P19/02; A61P19/06; A61P19/08; A61P19/10; A61P21/06; A61P25/28; A61P27/02; A61P27/16; A61P29/00; A61P31/12; A61P31/18; A61P35/00; A61P35/02; A61P37/06; A61P37/08; C07D401/12; C07D405/12; C07D409/12; C07D413/12; C07D417/12; C07D471/04**

- european: **C07D213/73F6; C07D213/75B8; C07D213/82H; C07D401/12; C07D405/12; C07D409/12; C07D413/12; C07D417/12; C07D471/04**

Application number: JP20000520418T 19981104**Priority number(s):** US19970064953P 19971107; US19980185119 19981103; WO1998US23510 19981104**Also published as:**

WO9924404 (A)



EP1028945 (A1)



US6022884 (A1)



CA2307552 (A1)



AU742442 (B2)

Report a data error [here](#)

Abstract not available for JP2001522834T

Abstract of corresponding document: **US6022884**

Selected novel substituted pyridine compounds are effective for prophylaxis and treatment of diseases, such as TNF- alpha , IL-1 beta , IL-6 and/or IL-8 mediated diseases, and other maladies, such as pain and diabetes. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving inflammation, pain, diabetes, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

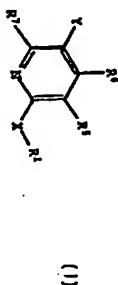
Data supplied from the **esp@cenet** database - Worldwide**BEST AVAILABLE COPY**

THIS PAGE BLANK (USPTO)

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:	A1		(11) International Publication Number:	WO 99/24404
C07D 21/373, 21/375, 21/382, A61K 31/44, C07D 41/312, 40/112, 40/912, 41/712, 41/104, 40/512		(43) International Publication Date:	20 May 1999 (2005/99)	
(21) International Application Number:	PCT/US99/2510		(21) Designated States:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, ES, FI, GR, GD, KZ, LC, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, SL, TI, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, European patent (GH, GI, KE, LS, MW, SD, SZ, UG, ZW), European patent (AM, AZ, BY, KG, KE, MD, RU, TI, TM), European patent (AT, BE, CH, CY, DE, DK, IS, EL, FR, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CO, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TO).
(22) International Filing Date:	4 November 1998 (94/11/98)		(22) Priority Date:	7 November 1997 (97/11/97) US 60/054,953 09/115,119
(71) Inventor:	MANTI, O, Nathan, B; 2518 Glamy Way, Lafayette, CO 80026 (US); SCHLAICHTER, Steven, J; 12482 Union Boulevard, Boulder, CO 80304 (US); JOSSEY, John, A.; 7173 Burgundy Drive, Longmont, CO 80503 (US).		(71) Applicant:	AMGEN INC. (US/US); One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).
(74) Agent:	ODRI, Steven, M, et al.; Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).			

(54) Title: SUBSTITUTED PYRIDINE COMPOUNDS AS ANTI-INFLAMMATORY AGENTS	(11)	Published
		With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.



(57) Abstract

Selected substituted pyridine compounds of formula (1) or a pharmaceutically acceptable salt thereof, wherein a, b, c, X is O, S, SC(O), SC(O)₂ or NR⁴, R¹ is a cycloalkyl, aryl, heterocyclyl or heteraryl radical which is optionally substituted by 1-4 radicals of alky, halo, haloalkyl, cyano, azido, nitro, amidino, R¹¹-Z¹¹- or R¹²-Z¹²-, provided that the total number of vinyl, heterocyclic, cycloalkyl and heterocyclic radicals in R¹ is 1-3; and provided that Y is -NR⁴-CO²-R⁶ and X is O or S, R³ is an aryl or heterocyclic radical which is optionally substituted by 1-3 radicals of alky, halo, haloalkyl, cyano, azido, nitro, amidino, R¹⁹-Z¹⁹- or R¹⁹-Z¹⁹-, provided that the total number of vinyl, heterocyclic, cycloalkyl and heterocyclic radicals in R³ is 1-3; and provided that Y is -CO²-NR⁴-R⁶, R⁶ is other than a phenyl or isopropyl having an amino, nitro, cyano, carbonyl or alkoxycarbonyl, are effective for prophylaxis and treatment of disease, such as TNF- α , IL-1 β , IL-6 and/or IL-8 mediated diseases, and other maladies, such as pain and diabetes. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies, or conditions involving inflammation, pain, diabetes, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

FOR THE PURPOSES OF INFORMATION ONLY

AL	ES	LA	LE	SI	SL
AM	FI	LT	Lithuania	SK	Slovenia
AU	FR	LU	Luxembourg	SN	Slovakia
AZ	GA	LV	Latvia	SZ	Senegal
BA	GB	MC	Monaco	TD	Switzerland
BB	GB	MD	Republic of Moldova	TC	Togo
BE	GR	MG	Madagascar	TI	Tuvalu
BG	GR	MK	The former Yugoslav	TM	Tunisia
BG	GR	MK	Republic of Macedonia	TR	Turkey
BG	HU	MU	Mauritius	TT	Trinidad and Tobago
BG	HU	MU	Mongolia	UA	Ukraine
BR	IR	MU	Morocco	UG	Uganda
BR	IR	MU	Morocco	US	United States of America
BY	IS	MU	Morocco	UZ	Uzbekistan
CA	IE	MU	Morocco	VN	Viet Nam
CA	JP	MU	Morocco	VU	Venezuela
CA	JP	MU	Morocco	ZW	Zimbabwe
CG	KR	NL	Netherlands		
CG	KR	NO	Norway		
CI	KR	NZ	New Zealand		
CI	KR	PL	Poland		
CM	KR	PT	Portugal		
CM	KR	PT	Portugal		
CO	KR	RO	Romania		
CO	KR	RU	Russia		
CO	KR	RU	Russia		
CZ	KR	RU	Russia		
CZ	KR	RU	Russia		
DE	LA	RU	Russia		
DE	LA	RU	Russia		
DK	LA	RU	Russia		
DK	LA	RU	Russia		
ES	LA	RU	Russia		
ES	LA	RU	Russia		

SUBSTITUTED PYRIDINE COMPOUNDS AS ANTI-INFLAMMATORY AGENTS

BACKGROUND OF THE INVENTION

5 The present invention comprises a new class of compounds useful in treating diseases, such as TNF- α , IL-1 β , IL-6 and/or IL-8 mediated diseases and other maladies, such as pain, cancer, and diabetes. In particular, the compounds of the invention are useful for the prophylaxis and treatment of diseases or conditions involving inflammation. This invention also relates to intermediates and processes useful in the preparation of such compounds.

10 Interleukin-1 (IL-1) and Tumor Necrosis Factor α (TNF- α) are pro-inflammatory cytokines secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli (e.g., lipopolysaccharide - LPS) or external cellular stress (e.g., osmotic shock and peroxides).

15 Elevated levels of TNF- α and/or IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; Paget's disease; osteophorosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic & cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; Reiter's syndrome; type I and type II diabetes; bone resorption diseases; graft vs. host reaction; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection.

20

25

30

35

HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster are also exacerbated by TNF- α . It has been reported that TNF- α plays a role in head trauma, stroke, and ischemia. For instance, in animal models of head trauma (rat), TNF- α levels increased in the contused hemisphere (Shohami et al., *J. Cereb. Blood Flow Metab.* **14**, 615 (1994)). In a rat model of ischemia wherein the middle cerebral artery was occluded, the levels of TNF- α mRNA of TNF- α increased (Reurstein et al., *Neurosci. Lett.* **164**, 125 (1993)). Administration of TNF- α into the rat cortex has been reported to result in significant neutrophil accumulation in capillaries and adherence in small blood vessels. TNF- α promotes the infiltration of other cytokines (IL-1 β , IL-6) and also chemokines, which promote neutrophil infiltration into the infarct area (Reurstein, *Stroke* **25**, 1481 (1994)). TNF- α has also been implicated to play a role in type II diabetes (Endocrinol. **130**, 43-52, 1994; and Endocrinol. **136**, 1474-1481, 1995).

10

15

20

25

30

35

40

45

50

55

60

65

70

75

80

85

90

95

100

105

110

115

120

125

130

135

140

145

150

155

160

165

170

175

180

185

190

195

200

205

210

215

220

225

230

235

240

245

250

255

260

265

270

275

280

285

290

295

300

305

310

315

320

325

330

335

340

345

350

355

360

365

370

375

380

385

390

395

400

405

410

415

420

425

430

435

440

445

450

455

460

465

470

475

480

485

490

495

500

505

510

515

520

525

530

535

540

545

550

555

560

565

570

575

580

585

590

595

600

605

610

615

620

625

630

635

640

645

650

655

660

665

670

675

680

685

690

695

700

705

710

715

720

725

730

735

740

745

750

755

760

765

770

775

780

785

790

795

800

805

810

815

820

825

830

835

840

845

850

855

860

865

870

875

880

885

890

895

900

905

910

915

920

925

930

935

940

945

950

955

960

965

970

975

980

985

990

995

1000

1005

1010

1015

1020

1025

1030

1035

1040

1045

1050

1055

1060

1065

1070

1075

1080

1085

1090

1095

1100

1105

1110

1115

1120

1125

1130

1135

1140

1145

1150

1155

1160

1165

1170

1175

1180

1185

1190

1195

1200

1205

1210

1215

1220

1225

1230

1235

1240

1245

1250

1255

1260

1265

1270

1275

1280

1285

1290

1295

1300

1305

1310

1315

1320

1325

1330

1335

1340

1345

1350

1355

1360

1365

1370

1375

1380

1385

1390

1395

1400

1405

1410

1415

1420

1425

1430

1435

1440

1445

1450

1455

1460

1465

1470

1475

1480

1485

1490

1495

1500

1505

1510

1515

1520

1525

1530

1535

1540

1545

1550

1555

1560

1565

1570

1575

1580

1585

1590

1595

1600

1605

1610

1615

1620

1625

1630

1635

1640

1645

1650

1655

1660

1665

1670

1675

1680

1685

1690

1695

1700

1705

1710

1715

1720

1725

1730

1735

1740

1745

1750

1755

1760

1765

1770

1775

1780

1785

1790

1795

1800

1805

1810

1815

1820

1825

1830

1835

1840

1845

1850

1855

1860

1865

1870

1875

1880

1885

1890

1895

1900

1905

1910

1915

1920

1925

1930

1935

1940

1945

1950

1955

1960

1965

1970

1975

1980

1985

1990

1995

2000

2005

2010

2015

2020

2025

2030

2035

2040

2045

2050

2055

2060

2065

2070

2075

2080

2085

2090

2095

2100

2105

2110

2115

2120

2125

2130

2135

2140

2145

2150

2155

2160

2165

2170

2175

2180

2185

2190

2195

2200

2205

2210

2215

2220

2225

2230

2235

2240

2245

2250

2255

2260

2265

2270

2275

2280

2285

2290

2295

2300

2305

2310

2315

2320

2325

2330

2335

2340

2345

2350

2355

2360

2365

2370

2375

2380

2385

2390

2395

2400

2405

2410

2415

2420

2425

2430

2435

2440

2445

2450

2455

2460

2465

2470

2475

2480

2485

2490

2495

2500

2505

2510

2515

2520

2525

2530

2535

2540

2545

2550

2555

2560

2565

2570

2575

2580

2585

2590

2595

2600

2605

2610

2615

2620

2625

2630

2635

2640

2645

2650

2655

2660

2665

2670

2675

2680

2685

2690

2695

2700

2705

2710

2715

2720

2725

2730

2735

2740

2745

2750

2755

2760

2765

2770

2775

2780

2785

2790

2795

2800

2805

2810

2815

2820

2825

2830

2835

2840

2845

2850

2855

2860

2865

2870

2875

2880

2885

2890

2895

2900

2905

2910

2915

2920

2925

2930

2935

2940

2945

2950

2955

2960

2965

2970

2975

2980

2985

2990

2995

3000

3005

3010

3015

3020

3025

3030

3035

3040

3045

3050

3055

3060

3065

3070

3075

3080

3085

3090

3095

3100

3105

3110

3115

3120

3125

3130

3135

3140

3145

3150

3155

3160

3165

3170

3175

3180

3185

3190

3195

3200

3205

3210

3215

3220

3225

3230

3235

3240

3245

3250

3255

3260

3265

3270

3275

3280

3285

3290

3295

3300

3305

3310

3315

3320

3325

3330

3335

3340

3345

3350

3355

3360

3365

3370

3375

3380

3385

3390

3395

3400

3405

3410

3415

3420

3425

3430

3435

3440

3445

3450

3455

3460

3465

3470

3475

3480

3485

3490

3495

3500

3505

3510

3515

3520

3525

3530

3535

3540

3545

3550

3555

3560

3565

3570

3575

3580

3585

3590

3595

3600

3605

3610

3615

3620

3625

3630

3635

3640

3645

3650

3655

3660

3665

3670

3675

3680

3685

3690

3695

3700

3705

3710

3715

3720

3725

3730

3735

3740

3745

3750

3755

3760

3765

3770

3775

3780

3785

3790

3795

3800

3805

3810

3815

3820

3825

3830

3835

3840

3845

3850

3855

3860

3865

3870

3875

3880

3885

3890

3895

3900

3905

3910

3915

3920

3925

3930

3935

3940

3945

3950

3955

3960

3965

3970

3975

3980

3985

3990

3995

4000

4005

4010

4015

4020

4025

4030

4035

4040

4045

4050

4055

4060

4065

4070

4075

4080

4085

4090

4095

4100

4105

4110

4115

4120

4125

4130

4135

4140

4145

4150

4155

4160

4165

4170

4175

4180

4185

4190

4195

4200

4205

4210

4215

4220

4225

4230

4235

4240

4245

4250

4255

4260

4265

4270

4275

4280

4285

4290

4295

4300

4305

4310

4315

4320

4325

4330

4335

4340

4345

4350

4355

4360

4365

4370

4375

4380

4385

4390

4395

4400

4405

4410

4415

4420

4425

4430

4435

4440

4445

4450

4455

4460

4465

4470

4475

4480

4485

4490

4495

4500

4505

4510

4515

4520

4525

4530

4535

4540

4545

4550

4555

4560

4565

4570

4575

4580

4585

4590

4595

4600

4605

4610

4615

4620

4625

4630

4635

4640

4645

4650

4655

4660

4665

4670

4675

4680

4685

4690

4695

4700

4705

4710

4715

4720

4725

4730

4735

4740

4745

4750

4755

4760

4765

4770

4775

4780

4785

4790

4795

4800

4805

4810

4815

4820

4825

4830

4835

4840

4845

4850

4855

4860

4865

4870

4875

4880

4885

4890

4895

4900

4905

4910

4915

4920

4925

4930

4935

4940

4945

4950

4955

4960

4965

4970

4975

4980

4985

4990

4995

5000

5005

5010

5015

5020

5025

5030

5035

5040

5045

5050

5055

5060

5065

5070

5075

5080

5085

5090

5095

5100

5105

5110

5115

5120

5125

5130

5135

5140

5145

5150

5155

5160

5165

5170

5175

5180

5185

5190

5195

5200

5205

5210

5215

5220

5225

5230

5235

5240

5245

5250

5255

5260

5265

5270

5275

5280

5285

5290

5295

5300

5305

5310

5315

5320

5325

5330

5335

5340

5345

5350

5355

5360

5365

5370

5375

5380

5385

5390

5395

5400

5405

5410

5415

5420

5425

5430

5435

5440

5445

5450

5455

5460

5465

5470

5475

5480

5485

5490

5495

5500

5505

5510

5515

5520

5525

5530

5535

5540

5545

5550

5555

5560

5565

5570

5575

5580

5585

5590

5595

5600

5605

5610

5615

5620

5625

5630

5635

5640

5645

5650

5655

5660

5665

5670

5675

5680

5685

5690

5695

5700

5705

5710

5715

5720

5725

5730

5735

5740

5745

5750

5755

5760

5765

5770

5775

5780

5785

5790

579

Elevated levels of IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; ulcerative colitis; anaphylaxis; muscle degeneration; cachexia; Reiter's syndrome; type I and type II diabetes; bone resorption diseases; ischemia-reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; sepsis; septic shock; and toxic shock syndrome. Viruses sensitive to TNF- α inhibition, e.g., HIV-1, HIV-2, HIV-3, are also affected by IL-1.

TNF- α and IL-1 appear to play a role in pancreatic β cell destruction and diabetes. Pancreatic β cells produce insulin which helps mediate blood glucose homeostasis. Deterioration of pancreatic β cells often accompanies type I diabetes. Pancreatic β cell functional abnormalities may occur in patients with type II diabetes. Type II diabetes is characterized by a functional resistance to insulin. Further, type II diabetes is also often accompanied by elevated levels of plasma glucagon and increased rates of hepatic glucose production. Glucagon is a regulatory hormone that attenuates liver gluconeogenesis inhibition by insulin. Glucagon receptors have been found in the liver, kidney and adipose tissue. Thus glucagon antagonists are useful for attenuating plasma glucose levels (WO 97/16442, incorporated herein by reference in its entirety). By antagonizing the glucagon receptors, it is thought that insulin responsiveness in the liver will improve, thereby decreasing gluconeogenesis and lowering the rate of hepatic glucose production.

In rheumatoid arthritis models in animals, multiple intra-articular injections of IL-1 have led to an acute and destructive form of arthritis (Chandrasekhar et al., Clinical Immunol Immunopathol. 55, 382 (1990)). In

studies using cultured rheumatoid synovial cells, IL-1 is a more potent inducer of stromelysin than is TNF- α (Firestein, Am. J. Pathol. 140, 1309 (1992)). At sites of local injection, neutrophil, lymphocyte, and monocyte emigration has been observed. The emigration is attributed to the induction of chemokines (e.g., IL-8), and the up-regulation of adhesion molecules (Dinarello, Eur. Cytokine Netw. 5, 517-531 (1994)).

IL-1 also appears to play a role in promoting certain viral life cycles. For example, cytokine-induced increase of HIV expression in a chronically infected macrophage line has been associated with a concomitant and selective increase in IL-1 production (Folks et al., J. Immunol. 136, 40 (1986)). Beutler et al. (J. Immunol. 135, 3969 (1985)) discussed the role of IL-1 in cachexia. Baracos et al. (New Eng. J. Med. 308, 553 (1983)) discussed the role of IL-1 in muscle degeneration.

In rheumatoid arthritis, both IL-1 and TNF- α induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue destruction within the arthritic joints. In a model of arthritis (collagen-induced arthritis (CIA) in rats and mice), intra-articular administration of TNF- α either prior to or after the induction of CIA led to an accelerated onset of arthritis and a more severe course of the disease (Brahn et al., Lymphokine Cytokine Res. 11, 253 (1992); and Cooper, Clin. Exp. Immunol. 898, 244 (1992)).

IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil infiltration into sites of inflammation or injury (e.g., ischemia) is mediated by the chemotactic nature of IL-8, including, but not limited to, the following: asthma, inflammatory bowel disease, psoriasis, adult respiratory distress syndrome, cardiac and renal reperfusion injury,

5

thrombosis and glomerulonephritis. In addition to the chemotaxis effect on neutrophils, IL-8 also has the ability to activate neutrophils. Thus, reduction in IL-8 levels may lead to diminished neutrophil infiltration. 5 Several approaches have been taken to block the effect of TNF- α . One approach involves using soluble receptors for TNF- α (e.g., TNFR-55 or TNFR-75), which have demonstrated efficacy in animal models of TNF- α -mediated disease states. A second approach to 10 neutralizing TNF- α using a monoclonal antibody specific to TNF- α , CA2, has demonstrated improvement in swollen joint count in a Phase II human trial of rheumatoid arthritis (Feldmann et al., *Immunological Reviews*, pp. 195-223 (1995)). These approaches block the effects of 15 TNF- α and IL-1 by either protein sequestration or receptor antagonism.

The present invention also relates to a method of treating cancer which is mediated by Raf and Raf-inducible proteins. Raf proteins are kinases activated in response to extracellular mitogenic stimuli such as PDGF, acidic FGF, thrombin, insulin or endothelin, and also in response to oncoproteins such as v-src, v-sis, and v-fms. Raf functions downstream of ras in 20 signal transduction from the cellular membrane to the nucleus. Compounds in the present invention may be 25 oncolytics. Raf functions downstream of ras in signal transduction from the cellular membrane to the nucleus. Antisense constructs which reduce cellular levels of c-Raf and hence Raf activity inhibit the growth of rodent fibroblasts in soft agar, while exhibiting little or no 30 general cytotoxicity. This inhibition of growth in soft agar is highly predictive of tumor responsiveness in whole animals. Moreover Raf antisense constructs have shown efficacy in reducing tumor burden in animals. Examples of cancers where Raf kinase is implicated by 35 overexpression include cancers of the brain, larynx, lung, lymphatic system, urinary tract and stomach,

6

including histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. Other examples include cancers involving overexpression of upstream activators of Raf or Raf-activating oncogenes, including pancreatic and 5 breast carcinoma.

Substituted imidazole and pyrrole compounds have been described for use in the treatment of cytokine mediated diseases by inhibition of proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF. 10 Substituted imidazoles for use in the treatment of cytokine mediated diseases have been described in US Pat. 5,593,992; WO 93/14081; WO 97/18626; WO 96/21452; WO 96/21654; WO 96/40143; WO 97/05878; WO 97/05878; (each of which is incorporated herein by reference in its entirety). Substituted imidazoles for use in the treatment of inflammation has been described in US Pat. 3,929,807 (which is incorporated herein by reference in its entirety). Substituted pyrrole compounds for use in the treatment of cytokine mediated diseases have been 15 described in WO 97/05877; WO 97/05878; WO 97/16426; WO 97/16441; and WO 97/16442 (each of which is incorporated herein by reference in its entirety).

Substituted 2-aminopyridine compounds have been 20 described as nitric oxide synthase inhibitors for use in the treatment of inflammation, neurodegenerative disorders and disorders of gastrointestinal motility in WO 96/18616 and WO 96/18617.

Diaryl substituted pyridine compounds have been 25 described for use in the treatment of inflammation and 30 inflammation related disorders in WO 96/24584 and US 5,596,008.

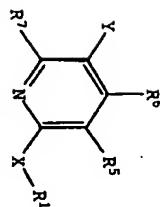
US 3,910,652, US 3,991,057 and US 4,002,629 describe piperazinyl substituted pyridine compounds for use as anti-inflammatory and cardiovascular agents. 35 JP 613934 describes substituted pyridine compounds as phospholipase A2 inhibitors for use as antiphlogistic and anti-pancreatitis agents. GB 1,189,188 describes

pyrimidin-2-ylamino substituted pyridine compounds as therapeutically valuable compounds for use as antiphlogistic agents.

5 BRIEF DESCRIPTION OF THE INVENTION

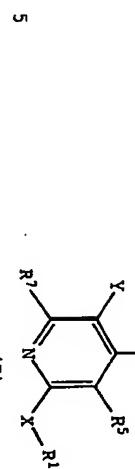
The present invention comprises a new class of compounds useful in the prophylaxis and treatment of diseases, such as TNF- α , IL-1 β , IL-6 and/or IL-8 mediated diseases and other maladies, such as pain, cancer, and diabetes. In particular, the compounds of the invention are useful for the prophylaxis and treatment of diseases or conditions involving inflammation. Accordingly, the invention also comprises pharmaceutical compositions comprising the compounds, methods for the prophylaxis and treatment of TNF- α , IL-1 β , IL-6 and/or IL-8 mediated diseases, such as inflammatory, pain and diabetes diseases, using the compounds and compositions of the invention, and intermediates and processes useful for the preparation of the compounds of the invention.

The compounds of the invention are represented by the following general structure:



wherein R¹, R², R³, R⁴, X and Y are defined below.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents and other publications recited herein are hereby incorporated by reference in their entirety.



or a pharmaceutically acceptable salt thereof, wherein

X is O, S, S(0), S(0), or NR²; preferably, X is O, S or

10 NR²; more preferably, X is O or NR²; most preferably, X is NR²;

Y is -C(O)-NR³R⁴ or -NR⁴-C(O)-R³;

15 R¹ is a cycloalkyl, aryl, heterocyclyl or heteroaryl radical which is optionally substituted by 1-4 radicals of alkyl, halo, haloalkyl, cyano, azido, nitro, amidino, R¹⁸-Z¹⁸- or R¹⁸-Z¹⁸-alkyl;

20 preferably, R¹ is a cycloalkyl, aryl, heterocyclyl or heteroaryl radical which is optionally substituted by 1-4 radicals of C₁-C₆ alkyl, halo, C₁-C₆ haloalkyl or 1-3 halo radicals, cyano, azido, nitro, amidino, R¹⁸-Z¹⁸- or R¹⁸-Z¹⁸-C₁-C₆ alkyl;

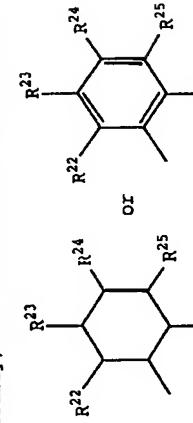
25 more preferably, R¹ is a cycloalkyl, aryl, heterocyclyl or heteroaryl radical which is optionally substituted by 1-4 radicals of C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl or 1-3

9

halo radicals, cyano, azido, nitro, amidino, $R^{18}-Z^{18}$ - or $R^{18}-Z^{18}-C_1-C_4$ alkyl;

provided that the total number of aryl, heteroaryl, 5 cycloalkyl and heterocyclyl radicals in R^1 is 1-3, preferably, 1-2, and provided when Y is $-NR^4-C(O)-R^3$ and X is 0 or S, R^1 is other than a 2-pyrimidinyl radical;

more preferably, R^1 is a radical of the formula



10 wherein R^{22} , R^{23} , R^{24} , R^{25} and R^{26} are each independently a radical of hydrogen, C_1-C_4 alkyl, halo, trifluoromethyl, cyano, azido, nitro, amidino, $R^{18}-Z^{18}$ - or $R^{18}-Z^{18}-C_1-C_4$ alkyl; provided at least one of R^1 , R^2 , R^3 , R^4 and R^{25} is hydrogen; and provided that the combined total number of aryl and heteroaryl radicals in R^1 , R^2 , R^3 , R^4 and R^{25} is 0-1;

15 R^2 is a hydrogen or alkyl radical; preferably, R^2 is a hydrogen or C_1-C_4 alkyl radical; more preferably, R^2 is a hydrogen or C_1-C_2 alkyl radical; more preferably, R^2 is a hydrogen or methyl radical; and most preferably, R^2 is a hydrogen radical;

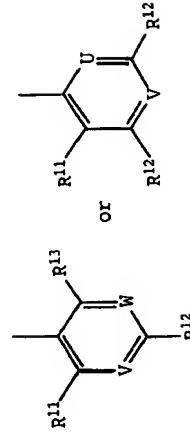
20 R^3 is an aryl or heteroaryl radical which is optionally substituted by 1-5 radicals of alkyl, halo, haloalkyl,

10

cyano, azido, nitro, amidino, $R^{19}-Z^{19}$ - or $R^{19}-Z^{19}-alkyl$; preferably, R^3 is an aryl or heteroaryl radical which is optionally substituted by 1-5 radicals of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl of 1-3 halo radicals, cyano, 5 azido, nitro, amidino, $R^{19}-Z^{19}$ - or $R^{19}-Z^{19}-C_1-C_6$ alkyl; more preferably, R^3 is an aryl or heteroaryl radical which is optionally substituted by 1-5 radicals of C_1-C_6 alkyl, halo, C_1-C_4 haloalkyl of 1-3 halo radicals, cyano, azido, nitro, amidino, $R^{19}-Z^{19}$ - or $R^{19}-Z^{19}-C_1-C_4$ alkyl;

10 provided that the total number of aryl and heteroaryl radicals in R^3 is 1-3, preferably, 1-2; and provided when Y is $-C(O)-NR^4-R^3$ where Y is naphthyl having an amino, nitro, cyano, carboxy or alkoxy carbonyl substituent bonded to the ring carbon atom adjacent to the ring carbon atom bonded to $-NR^4-$;

more preferably, R^3 is a radical of the formula



20

wherein

U is $C-R^{13}$ or N;

25 V and W are each independently $C-R^{12}$ or N;

R^{11} and R^{13} are each independently a radical of hydrogen, C₁-C₄ alkyl, halo, trifluoromethyl, cyano, azido, nitro, amidino or R^{19} -Z¹⁹-; preferably, R^{11} and R^{13} are each independently a radical of hydrogen, methyl, ethyl, fluoro, chloro, trifluoromethyl, cyano, azido, nitro, amidino, R^{19} -O-, R^{19} -S(O)₂-, R^{19} -O-C(O)-, R^{19} -C(O)-, R^{19} -NR²¹-C(O)- or R^{19} -NR²¹-S(O)₂-;

each R^{12} is independently a radical of hydrogen, C₁-C₆ alkyl, halo, C₁-C₄ haloalkyl of 1-3 halo radicals, R^{31} -Z³¹- or R^{31} -C₁-C₄ alkyl; preferably, each R^{12} is independently a radical of hydrogen, methyl, ethyl, fluoro, chloro, trifluoromethyl, trifluoromethoxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, aminocarbonyl, dimethylaminocarbonyl, aminomethyl, (methylamino)methyl or (dimethylamino)methyl;

provided that the combined total number of aryl and heteroaryl radicals in R^{11} , R^{12} and R^{13} is 0-1;

wherein each R^{31} is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy;

each Z^{31} is independently -O-, -NR²¹-, -NR²¹-C(O)-, -C(O)-NR²¹-, -NR²¹-S(O)₂- or -S(O)₂-NR²¹;

R^4 is a hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or R^{20} -Z²⁰-alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of hydroxy, alkoxy, alkylthiol, amino, alkylamino, dialkylamino, alkanoylamino, alkylsulfonylamino, alkylsulfinyl, alkylsulfonyl, alkoxycarbonylamino, alkoxycarbonyl, cyano, halo, azido, alkyl, haloalkyl or haloalkoxy;

10 preferably, R^4 is a radical of hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ haloalkyl of 1-3 halo radicals, C₂-C₆ haloalkenyl of 1-3 halo radicals, aryl, heteroaryl, aryl-C₁-C₄ alkyl, heteroaryl-C₁-C₄ alkyl or R^{20} -Z²⁰-C₁-C₆ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of hydroxy, C₁-C₄ alkoxylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, C₁-C₆ alkanoylamino, C₁-C₄ alkylsulfonylamino, C₁-C₄ alkylsulfinyl, C₁-C₄ alkoxylcarbonyl, cyano, halo, azido, C₁-C₄ alkyl, C₁-C₄ haloalkyl of 1-3 halo radicals or C₁-C₄ haloalkoxy of 1-3 halo radicals;

25 more preferably, R^4 is a radical of hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl, heteroaryl-C₁-C₄ alkyl or R^{20} -Z²⁰-C₂-C₆ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, C₁-C₄ alkoxylthiol, amino, alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, acetylamino, halo, C₁-C₄ alkyl, trifluoromethyl or trifluoromethoxy;

more preferably, R^4 is a radical of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, $aryl-C_1-C_4$ alkyl, heteroaryl- C_1-C_4 alkyl or $R^{20-2}-C_2-C_4$ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, methylthiol, ethylthiol, amino, methylamino, dimethylamino, ethylamino, diethylamino, acetylamino, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy;

more preferably, R^4 is a radical of hydrogen, methyl or ethyl radical;

preferably, each R^8 is independently a hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl of 1-3 halo radicals, aryl, heteroaryl, aryl- C_1-C_4 alkyl or heteroaryl- C_1-C_4 alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkylthiol, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, C_1-C_5 alkanoylamino, C_1-C_4 alkylsulfonylamino, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, $(C_1-C_4$ alkoxyl)carbonylamino, $(C_1-C_4$ alkoxyl)carbonyl, cyano, halo, azido, C_1-C_4 alkyl, C_1-C_4 haloalkyl of 1-3 halo radicals or C_1-C_4 haloalkoxy of 1-3 halo radicals;

more preferably, each R^{18} is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₂ alkyl or heteroaryl-C₁-C₂ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, acetylaminino, cyano, halo, azido, C₁-C₄ alkyl, trifluoromethyl or trifluoromethoxy;

10 each Z^{18} is independently $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-$
 CO_2- , $-C(O)-$, $-NR^{21}-$, $-NR^{21}-C(O)-$, $-C(O)-NR^{21}-$, $-NR^{21}-$
 $S(O)_2-$ or $-S(O)_2-NR^{21}-$; preferably, each Z^{18} is
 independently $-O-$, $-S-$, $-S(O)_2-$, $-CO_2-$, $-NR^{21}-$, $-NR^{21}-$
 $C(O)-$, $-C(O)-NR^{21}-$, $-NR^{21}-S(O)_2-$ or $-S(O)_2-NR^{21}-$;

15 wherein each R^{19} is independently a hydrogen, alkyl,
 haloalkyl, aryl, heteroaryl, arylalkyl or
 heteroarylalkyl radical, wherein the aryl and heteroaryl
 20 radicals are optionally substituted by 1-3 radicals of
 hydroxy, alkoxy, alkylthiol, amino, alkylamino,
 dialkylamino, alkanoylamino, alkylsulfonylamino,
 alkylsulfinyl, alkylsulfonyl, alkoxycarbonylamino,
 alkoxy carbonyl, cyano, halo, azido, alkyl, haloalkyl or
 25 haloalkoxy;

30 preferably, each R^{19} is independently a hydrogen, C_1-C_4
 alkyl, C_1-C_4 haloalkyl of 1-3 halo radicals, aryl,
 heteroaryl, $aryl-C_1-C_4$ alkyl or heteroaryl- C_1-C_4 alkyl
 radical, wherein the aryl and heteroaryl radicals are
 35 optionally substituted by 1-3 radicals of hydroxy, C_1-C_4
 alkoxy, C_1-C_4 alkylthiol, amino, C_1-C_4 alkanoylamino, C_1-C_4
 alkylsulfonylamino, C_1-C_4 alkylsulfinyl, C_1-C_4

15

16

alkylsulfonyl, (C₁-C₄ alkoxy)carbonylamino, (C₁-C₄ alkoxy)carbonyl, cyano, halo, azido, C₁-C₄ alkyl, C₁-C₄ haloalkyl of 1-3 halo radicals or C₁-C₄ haloalkoxy of 1-3 halo radicals;

5

more preferably, each R¹⁹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, cyano, halo, C₁-C₄ alkyl, alkylamino, acetylamino, cyano, halo, C₁-C₄ alkyl, trifluoromethyl or trifluoromethoxy;

15

more preferably, each R¹⁹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy;

20

more preferably, each R¹⁹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, phenyl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy;

25

more preferably, each R¹⁹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, phenyl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, fluoro, chloro, methyl, ethyl, trifluoromethyl or trifluoromethoxy;

30

more preferably, each R¹⁹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, phenyl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino,

independently -O-, -S(O)₂-, -CO₂-, -C(O)-, -NR²¹-C(O)-, -NR²¹-C(O)O-, -NR²¹-S(O)₂-, or -S(O)₂-NR²¹-; more preferably, each Z¹⁹ is independently -O-, -S(O)₂-, -O-C(O)-, -C(O)-, -NR²¹-C(O)O- or -NR²¹-S(O)₂-,

5

10

wherein each R²⁰ is independently a hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of hydroxy, alkoxy, alkylthiol, amino, alkylamino, dialkylamino, alkanoylamino, alkylsulfonylamino, alkylsulfinyl, alkylsulfonyl, alkoxycarbonylamino, alkoxycarbonyl, cyano, halo, azido, alkyl, haloalkyl or haloalkoxy;

15

20

preferably, each R²⁰ is independently a hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl of 1-3 halo radicals, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonylamino, C₁-C₄ alkoxy)carbonylamino, (C₁-C₄ alkoxy)carbonyl, cyano, halo, azido, C₁-C₄ alkyl, C₁-C₄ haloalkyl of 1-3 halo radicals or C₁-C₄ haloalkoxy of 1-3 halo radicals;

25

more preferably, each R²⁰ is independently a hydrogen, C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₂ alkyl or heteroaryl-C₁-C₂ alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino,

17

acetylamino, halo, C_1 - C_4 alkyl, trifluoromethyl or trifluoromethoxy;

more preferably, each R^{20} is independently a hydrogen, 5 C_1 - C_4 alkyl, aryl, heteroaryl, aryl- C_1 - C_2 alkyl or heteroaryl- C_1 - C_2 alkyl radical, wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, methylthio, ethylthiol, amino, methylamino, dimethylamino, 10 ethylamino, diethylamino, acetylamino, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy;

each z^{20} is independently -0-, -S-, -S(O)₂-, -
 CO_2 -, -C(O)-, -NR²¹-, -NR²¹-C(O)-, -C(O)-NR²¹-, -NR²¹-
 15 S(O)₂-, or -S(O)₂-NR²¹-, preferably, each z^{20} is independently -0- or -NR²¹-,

wherein each R^{21} is independently a hydrogen or alkyl radical; preferably, each R^{21} is independently a hydrogen radical; more preferably, each R^{21} is 20 or C_1 - C_4 alkyl radical; more preferably, each R^{21} is independently a hydrogen or methyl radical;

R^5 and R^6 are each independently a haloalkyl, 25 dialkylaminohalkyl, amino, alkylamino, dialkylamino, alkanoyleamino, alkylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, hydroxy, hydroxylalkyl, thiol, alkylthiol, alkylsulfinyl, alkylsulfonyl, alkoxylalkyl, cyano, azido, nitro, 30 carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl radical;

preferably, R^5 and R^6 are each independently a hydrogen, C_1 - C_4 alkyl, halo, C_1 - C_4 haloalkyl of 1-3 halo radicals,

18

C_1 - C_4 haloalkoxy of 1-3 halo radicals, C_1 - C_4 aminooalkyl, (C_1 - C_4 alkyl)amino- C_1 - C_4 alkyl, di(C_1 - C_4 alkyl)amino, di(C_1 - C_4 alkyl)amino- C_1 - C_4 alkyl, 5 C_1 - C_5 alkanoylamino, C_1 - C_4 alkylaminosulfonyl, di(C_1 - C_4 alkyl)aminosulfonyl, C_1 - C_4 alkylaminosulfonyl, di(C_1 - C_4 alkyl)aminosulfonyl, hydroxy, C_1 - C_4 hydroxyalkyl, thiol, C_1 - C_4 alkylthiol, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkylsulfonyl, C_1 - C_4 alkoxyl, (C_1 - C_4 alkyl)alkoxy, C_1 - C_4 alkyl, 10 cyano, azido, nitro, carboxy, (C_1 - C_4 alkyl)aminocarbonyl or di(C_1 - C_4 alkyl)aminocarbonyl radical;

more preferably, R^5 and R^6 are each independently a hydrogen, C_1 - C_4 alkyl, halo, trifluoromethyl, 15 trifluoromethoxy, amino, C_1 - C_4 alkylamino, di(C_1 - C_4 alkyl)amino, C_1 - C_5 alkanoylamino, hydroxy, C_1 - C_4 hydroxylalkyl, C_1 - C_4 alkoxyl, cyano, azido, nitro, carboxy, (C_1 - C_4 alkyl)aminocarbonyl or di(C_1 - C_4 alkyl)aminocarbonyl radical;

more preferably, R^5 and R^6 are each independently a hydrogen, methyl, ethyl, halo, trifluoromethyl, trifluoromethoxy, amino, C_1 - C_2 alkylamino, di(C_1 - C_2 alkyl)amino, hydroxy, methoxy or ethoxy radical; most preferably, R^5 and R^6 are each a hydrogen radical; 20 R^7 is a hydrogen, alkyl, halo, haloalkyl, haloalkoxy, aminooalkyl, alkylaminooalkyl, dialkylaminooalkyl, 25 aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, hydroxy, hydroxylalkyl, thiol, alkylthiol, alkylsulfinyl, alkylsulfonyl, alkoxylalkyl, cyano, azido, nitro, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl radical;

preferably, R^5 and R^6 are each independently a hydrogen, C_1 - C_4 alkyl, halo, C_1 - C_4 haloalkyl of 1-3 halo radicals,

preferably, R' is a hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl of 1-3 halo radicals, C₁-C₄ haloalkoxy of 1-3 halo radicals, C₁-C₄ aminosalkyl, (C₁-C₄ alkyl)amino-C₁-C₄ alkyl, di(C₁-C₄ alkyl)aminosulfonyl, C₁-C₄ alkylaminosulfonyl, di(C₁-C₄ alkyl)aminosulfonyl, hydroxy, C₁-C₄ hydroxylalkyl, thiol, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkoxy(C₁-C₄ alkyl, cyano, azido, nitro, carboxy, (C₁-C₄ alkoxy)carbonyl, aminocarbonyl, (C₁-C₄ alkyl)aminocarbonyl or di(C₁-C₄ alkyl)aminocarbonyl radical;

more preferably, R' is a hydrogen, C₁-C₄ alkyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, C₁-C₄ hydroxylalkyl, C₁-C₄ alkoxy, carbonyl, (C₁-C₄ alkoxy)carbonyl, aminocarbonyl, (C₁-C₄ alkyl)aminocarbonyl or di(C₁-C₄ alkyl)aminocarbonyl radical;

more preferably, R' is a hydrogen, methyl, ethyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, methoxy or ethoxy radical; most preferably, R' is a hydrogen radical.

The compounds of this invention may have in general several asymmetric centers and are typically depicted in the form of racemic mixtures. This invention is intended to encompass racemic mixtures, partially racemic mixtures and separate enantiomers and diastereomers.

Compounds of interest include the following:

2-cyclohexyloxy-5-(2,6-dichlorophenylcarbonylamino)pyridine;

2-cyclohexyloxy-5-(2-methylphenylcarbonylamino)pyridine;

2-(2,4-dimethylphenoxy)-5-(2-chlorophenylcarbonylamino)pyridine;

2-(2,4-dimethylphenoxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine;

2-(2,4-dimethylphenoxy)-5-(2-methylphenylcarbonylamino)pyridine;

2-(2,4-dimethylphenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;

2-(2,6-dimethyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;

2-(2-methyl-4-fluorophenoxy)-5-(2-methylphenylcarbonylamino)pyridine;

2-(2-methyl-4-chlorophenoxy)-5-(2-chlorophenylcarbonylamino)pyridine;

2-(2-methyl-4-chlorophenoxy)-5-(2-methylphenylcarbonylamino)pyridine;

2-(2-methylphenylcarbonylamino)pyridine;

2-(2-methylphenylcarbonylamino)pyridine;

2-(2-methyl-4-chlorophenoxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine;

2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;

2-(2-methyl-4-fluorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;

2-(2-methyl-4-fluorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;

2-(2-methyl-4-fluorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;

21

2- (2-methyl-4-fluorophenoxy) -5- (2-fluorophenylcarbonyl amino) pyridine;

2- (2, 4-dimethylphenoxy) -5- (2, 6-dimethylphenylcarbonyl amino) pyridine;

5 2- (1-naphthoxy) -5- (2-methylphenylcarbonyl amino) pyridine;

2- (1-naphthoxy) -5- (2, 6-dimethylphenylcarbonyl amino) pyridine;

10 2- (1-naphthoxy) -5- (2, 6-dimethylphenylcarbonyl amino) pyridine;

2- (2-methyl-3-pyridoxy) -5- (2, 6-dichlorophenylcarbonyl amino) pyridine;

2- (2-methyl-4-chlorophenoxy) -5- ((3, 5-dimethyl-4-isoxazolyl) carbonyl amino) pyridine;

15 2- (2-methyl-4-chlorophenylthio) -5- (2-methylphenylcarbonyl amino) pyridine;

2- (2-methyl-4-chlorophenylthio) -5- (2, 6-dimethylphenylcarbonyl amino) pyridine;

20 2-cyclohexylamino-5- (2, 6-dichlorophenylcarbonyl amino) pyridine;

2- (2-methylcyclohexylamino) -5- (2, 6-dichlorophenylcarbonyl amino) pyridine;

25 2- (2-methylcyclohexylamino) -5- (2-methylphenylcarbonyl amino) pyridine;

2- (2, 4-dimethylphenylamino) -5- (2-fluorophenylcarbonyl amino) pyridine;

30 2- (2, 4-dimethylphenylamino) -5- (2-chlorophenylcarbonyl amino) pyridine;

2- (2, 4-dimethylphenylamino) -5- (2, 6-dichlorophenylcarbonyl amino) pyridine;

35 2- (2, 4-dimethylphenylamino) -5- (2-methylphenylcarbonyl amino) pyridine;

22

2- (2-methylphenylamino) -5- (2-methylphenylcarbonyl amino) pyridine;

2- (2-methylphenylamino) -5- (2, 6-dichlorophenylcarbonyl amino) pyridine;

5 2- (2-methylphenylamino) -5- (2, 6-dimethylphenylcarbonyl amino) pyridine;

2- (2, 4-dimethylphenylamino) -5- (2, 6-dimethylphenylcarbonyl amino) pyridine;

10 carbonyl amino) pyridine;

2- (2-methyl-4-chlorophenylamino) -5- (2, 6-dimethylphenyl carbonyl amino) pyridine; and

2- (2-methyl-4-chlorophenylamino) -5- (2-methylphenyl aminocarbonyl) pyridine.

15 As utilized herein, the following terms shall have the following meanings:

20 "Alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing preferably 1-15 carbon atoms (C₁-C₁₅), more preferably 1-8 carbon atoms (C₁-C₈), even more preferably 1-6 carbon atoms (C₁-C₆), yet more preferably 1-4 carbon atoms (C₁-C₄), still more preferably 1-3 carbon atoms (C₁-C₃), and most preferably 1-2 carbon atoms (C₁-C₂). Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the like.

25 "Hydroxyl", alone or in combination, means an alkyl radical as defined above wherein at least one hydrogen radical is replaced with a hydroxyl radical, preferably 1-3 hydrogen radicals are replaced by hydroxyl radicals, more preferably 1-2 hydrogen radicals are replaced by hydroxyl radicals, and most preferably one hydrogen radical is replaced by a hydroxyl radical. Examples of such radicals include hydroxymethyl, 1-, 2-hydroxyethyl,

23

1-, 2-, 3-hydroxypropyl, 1,3-dihydroxy-2-propyl, 1,3-dihydroxybutyl, 1,2,3,4,5,6-hexahydroxy-2-hexyl and the like.

5 "Alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds, preferably 1-2 double bonds and more preferably one double bond, and containing

preferably 2-15 carbon atoms (C₂-C₁₅), more preferably 10 2-8 carbon atoms (C₂-C₈), even more preferably 2-6 carbon atoms (C₂-C₆), yet more preferably 2-4 carbon

atoms (C₂-C₄), and still more preferably 2-3 carbon atoms (C₂-C₃). Examples of such alkenyl radicals

15 include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like.

"Alkoxy", alone or in combination, means a radical of the type "R-O-", wherein "R" is an alkyl radical as defined above and "O" is an oxygen atom. Examples of

20 such alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

"Alkoxy carbonyl", alone or in combination, means a radical of the type "R-O-C(O)-" wherein "R" is an alkyl

25 radical of the type "R-O-C(O)-" wherein "R-O-" is an alkoxy radical as defined above and "C(O)" is a carbonyl radical of the type "R-O-C(O)-" wherein "R-O-" is an alkoxy radical as defined above and "C(O)" is a carbonyl radical.

"Alkylsulfinyl", alone or in combination, means a radical of the type "R-S(O)₁-", wherein "R" is an alkyl radical as defined above and "S(O)₁" is a di-oxygenated

30 sulfur atom. Examples of such alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, isopropylsulfinyl, n-butylsulfinyl, iso-butylsulfinyl, sec-butylsulfinyl, tert-butylsulfinyl and the like.

"Alkylsulfonyl", alone or in combination, means a radical of the type "R-S(O)₂-", wherein "R" is an alkyl radical as defined above and "S(O)₂" is a di-oxygenated

35 sulfur atom. Examples of such alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, iso-butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl and the like.

24

defined above and "S" is a sulfur atom. Examples of such alkylthio radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio and the like.

5 "Alkylsulfinyl", alone or in combination, means a radical of the type "R-S(O)₁-", wherein "R" is an alkyl radical as defined above and "S(O)₁" is a mono-oxygenated

10 sulfur atom. Examples of such alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, isopropylsulfinyl, n-butylsulfinyl, iso-butylsulfinyl, sec-butylsulfinyl, tert-butylsulfinyl and the like.

"Alkylsulfonyl", alone or in combination, means a radical of the type "R-S(O)₂-", wherein "R" is an alkyl radical as defined above and "S(O)₂" is a di-oxygenated

20 sulfur atom. Examples of such alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, iso-butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl and the like.

"Aryl", alone or in combination, means a phenyl or biphenyl radical, which is optionally benzo fused or heterocyclo fused and which is optionally substituted

25 with one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, azido, nitro, cyano,

haloalkyl, carboxy, alkoxy carbonyl, cycloalkyl, alkanoyl amino, amido, amidino, alkoxy carbonyl amino, N-alkylamidino, alkylamino, dialkylamino, aminoalkyl,

30 alkylaminoalkyl, dialkylaminoalkyl, N-alkylamido, N,N-dialkylamido, aralkoxy carbonyl amino, alkylthio, alkylsulfinyl, alkylsulfonyl, oxo and the like.

Examples of aryl radicals are phenyl, o-tolyl, 4-methoxyphenyl, 2-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 2-CF₃-phenyl, 2-fluorophenyl, 2-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 2-amino-3-(aminomethyl)phenyl, 6-

35

"Alkylthio", alone or in combination, means a radical of the type "R-S-", wherein "R" is an alkyl radical as

25

methyl-3-acetamidophenyl, 6-methyl-2-aminophenyl, 6-methyl-2,3-diaminophenyl, 2-amino-3-methylphenyl, 4,6-dimethyl-2-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 4-(2-methoxyphenyl)phenyl, 2-amino-1-naphthyl, 2-naphthyl, 3-amino-2-naphthyl, 1-methyl-3-amino-2-naphthyl, 2,3-diamino-1-naphthyl, 4,8-dinethoxy-2-naphthyl and the like.

"Aralkyl" and "aryalkyl", alone or in combination, means an alkyl radical as defined above in which at least one hydrogen atom, preferably 1-2, is replaced by an aryl radical as defined above, such as benzyl, 1-, 2-phenylethyl, dibenzylmethyl, hydroxyphenylmethyl, methylphenylmethyl, diphenylmethyl and the like.

"Aralkoxy", alone or in combination, means an alkoxy radical as defined above in which at least one hydrogen atom, preferably 1-2, is replaced by an aryl radical as defined above, such as benzylxy, 1-, 2-phenylethoxy, dibenzylmethoxy, hydroxyphenylmethoxy, methylphenylmethoxy, dichlorophenylmethoxy, 4-methoxyphenylmethoxy and the like.

"Aralkoxycarbonyl", alone or in combination, means a radical of the type "R-O-C(0)-" wherein "R-O-" is an aralkoxy radical as defined above and "-C(0)-" is a carbonyl radical.

"Alkanoyl", alone or in combination, means a radical of the type "R-C(0)-" wherein "R" is an alkyl radical as defined above and "-C(0)-" is a carbonyl radical. Examples of such alkanoyl radicals include acetyl, trifluoroacetyl, hydroxyacetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like.

26

"Alkanoylamino", alone or in combination, means a radical of the type "R-C(0)-NH-" wherein "R-C(0)-" is an alkanoyl radical as defined above, wherein the amino radical may optionally be substituted, such as with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl and the like.

"Aminocarbonyl", alone or in combination, means an amino substituted carbonyl (carbamoyl) radical, wherein the amino radical may optionally be mono- or di-substituted, such as with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyl, alkanoyl, alkoxy carbonyl, aralkoxycarbonyl and the like.

"Aminosulfonyl", alone or in combination, means an amino substituted sulfonyl radical.

"Benzo", alone or in combination, means the divalent radical C₆H₄ derived from benzene. "Benzo fused" forms 10 a ring system in which benzene and a cycloalkyl or aryl group have two carbons in common, for example tetrahydronaphthylene and the like.

"Bicyclic" as used herein is intended to include both fused ring systems, such as naphthyl and β -carbonyl, and substituted ring systems, such as biphenyl, phenylpyridyl and diphenylpiperazinyl.

"Cycloalkyl", alone or in combination, means a saturated or partially saturated, preferably one double bond, monocyclic, bicyclic or tricyclic carbocyclic alkyl radical, preferably monocyclic, containing preferably 5-12 carbon atoms (C₅-C₁₂), more preferably 5-10 carbon atoms (C₅-C₁₀), even more preferably 5-7 carbon atoms (C₅-C₇), which is optionally benzo fused or heterocyclo fused and which is optionally substituted as defined herein with respect to the definition of aryl. Examples

10 15 20 25 30 35

means an alkyl radical as defined above in which at least one hydrogen atom, preferably 1-2, is replaced by an aryl radical as defined above, such as benzyl, 1-, 2-phenylethyl, dibenzylmethoxy, hydroxyphenylmethoxy, methylphenylmethoxy, dichlorophenylmethoxy, 4-methoxyphenylmethoxy and the like.

"Aralkoxy", alone or in combination, means an alkoxy radical as defined above in which at least one hydrogen atom, preferably 1-2, is replaced by an aryl radical as defined above, such as benzylxy, 1-, 2-phenylethoxy, dibenzylmethoxy, hydroxyphenylmethoxy, methylphenylmethoxy, dichlorophenylmethoxy, 4-methoxyphenylmethoxy and the like.

"Aralkoxycarbonyl", alone or in combination, means a radical of the type "R-O-C(0)-" wherein "R-O-" is an aralkoxy radical as defined above and "-C(0)-" is a carbonyl radical.

"Alkanoyl", alone or in combination, means a radical of the type "R-C(0)-" wherein "R" is an alkyl radical as defined above and "-C(0)-" is a carbonyl radical. Examples of such alkanoyl radicals include acetyl, trifluoroacetyl, hydroxyacetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like.

27

28

of such cycloalkyl radicals include cyclopentyl, cyclohexyl, dihydroxycyclohexyl,

ethylenedioxycyclohexyl, cycloheptyl, octahydronaphthyl,

tetrahydronaphthyl, octahydroquinolinyl,

5 dimethoxytetrahydronaphthyl, 2,3-dihydro-1H-indenyl,

azabicyclo[3.2.1]octyl and the like.

"Heteroatoms" means nitrogen, oxygen and sulfur heteroatoms.

10 "Heterocyclo fused" forms a ring system in which a heterocyclyl or heteroaryl group of 5-6 ring members and a cycloalkyl or aryl group have two carbons in common, for example indole, isoquinoline, tetrahydroquinoline,

15 methylenedioxybenzene and the like.

"Heterocyclyl" means a saturated or partially unsaturated, preferably one double bond, monocyclic or

bicyclic, preferably monocyclic, heterocycle radical containing at least one, preferably 1 to 4, more

preferably 1 to 3, even more preferably 1-2, nitrogen, oxygen or sulfur atom ring member and having preferably

3-8 ring members in each ring, more preferably 5-8 ring members in each ring and even more preferably 5-6 ring

25 members in each ring. "Heterocyclyl" is intended to include sulfone and sulfoxide derivatives of sulfur ring

members and N-oxides of tertiary nitrogen ring members, and carbocyclic fused, preferably 3-6 ring carbon atoms

and more preferably 5-6 ring carbon atoms, and benzo

30 fused ring systems. "Heterocyclyl" radicals may optionally be substituted on at least one, preferably 1-

4, more preferably 1-3, even more preferably 1-2, carbon atoms by halogen, alkyl, alkoxy, hydroxy, oxo, thioxo,

aryl, aralkyl, heteroaryl, heteroaralkyl, amidino, N-

35 alkylamidino, alkoxycarbonylamino, alkylsulfonylamino and the like, and/or on a secondary nitrogen atom by hydroxy, alkyl, aralkoxycarbonyl, alkanoyl,

alkoxycarbonyl, heteroaralkyl, aryl or aralkyl radicals. More preferably, "heterocyclyl", alone or in combination, is a radical of a monocyclic or bicyclic saturated heterocyclic ring system having 5-8 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally partially unsaturated or benzo-fused and optionally substituted by 1-2 oxo or thioxo radicals. Examples of such heterocyclyl radicals include pyrrolidinyl,

10 piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 4-benzyl-piperazin-1-yl, pyrimidinyl, tetrahydrafuryl, pyrazolidinyl, pyrazolinyl, pyridazinonyl, pyrrolidonyl, tetrahydrothienyl and its sulfoxide and sulfone derivatives, 2,3-dihydroindolyl, tetrahydroquinolinyl, 15 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydro-1-oxo-isouquinolinyl, 2,3-dihydrobenzofuryl, benzopyranyl, methylenedioxyphenyl, ethylenedioxyphenyl and the like.

"Heteroaryl" means a monocyclic or bicyclic, preferably

20 monocyclic, aromatic heterocycle radical, having at least one, preferably 1 to 4, more preferably 1 to 3, even more preferably 1-2, nitrogen, oxygen or sulfur atom ring members and having preferably 5-6 ring members

25 in each ring, which is optionally saturated carbocyclic fused, preferably 3-4 carbon atoms (C₃-C₄) to form 5-6 ring numbered rings and which is optionally substituted as defined above with respect to the definitions of aryl. Examples of such heteroaryl groups include

imidazolyl, 1-benzylloxycarbonylimidazol-4-yl, pyrrolyl, 30 pyrazolyl, pyridyl, 3-(2-methyl)pyridyl, 3-(4-trifluoromethyl)pyridyl, pyrimidinyl, 5-(4-trifluoromethyl)pyrimidinyl, pyrazinyl, triazolyl, furyl, thiényl, oxazolyl, thiazolyl, indolyl, quinolinyl, 5,6,7,8-tetrahydroquinolinyl, quinoxalinyl,

35 5,6,7,8-tetrahydroisoquinolinyl, benzothiazolyl, benzofuryl, benzimidazolyl, benzoxazolyl and the like.

29

"Heteroalkyl" and "heteroarylalkyl," alone or in combination, means an alkyl radical as defined above in which at least one hydrogen atom, preferably 1-2, is replaced by a heteroaryl radical as defined above, such as 3-furylpropyl, 2-pyrrolyl propyl, chloroquinolinylmethyl, 2-thienylethyl, pyridylmethyl, 1-imidazolylethyl and the like.

10 "Halogen" and "halo", alone or in combination, means fluoro, chloro, bromo or iodo radicals.

"Haloalkyl", alone or in combination, means an alkyl radical as defined above in which at least one hydrogen atom, preferably 1-3, is replaced by a halogen radical, more preferably fluoro or chloro radicals. Examples of such haloalkyl radicals include 1,1,1-trifluoroethyl, chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, bis(trifluoromethyl)methyl and the like.

"Pharmacologically acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline earth, ammonium, quaternary ammonium cations and the like. For

30

additional examples of "pharmacologically acceptable salts," see *infra* and Berge et al, *J. Pharm. Sci.* **66**, 1 (1977).

5 "Cytokine" means a secreted protein that affects the functions of other cells, particularly as it relates to the modulation of interactions between cells of the immune system or cells involved in the inflammatory response. Examples of cytokines include but are not limited to interleukin 1 (IL-1), preferably IL-1 β , interleukin 6 (IL-6), interleukin 8 (IL-8) and TNF, preferably TNF- α (tumor necrosis factor- α).

10 "TNF, IL-1, IL-6, and/or IL-8 mediated disease or disease state" means all disease states wherein TNF, IL-1, IL-6, and/or IL-8 plays a role, either directly as TNF, IL-1, IL-6, and/or IL-8 itself, or by TNF, IL-1, IL-6, and/or IL-8 inducing another cytokine to be released. For example, a disease state in which IL-1 plays a major role, but in which the production of or action of IL-1 is a result of TNF, would be considered mediated by TNF.

15 "Leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

20 "Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the

35

25 acceptable salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline earth, ammonium, quaternary ammonium cations and the like. For

30 "Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the

31

32

31

like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include, but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl, alkyl, alky, substituted alkyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkenylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups include benzyloxycarbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example,

aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-buyl.

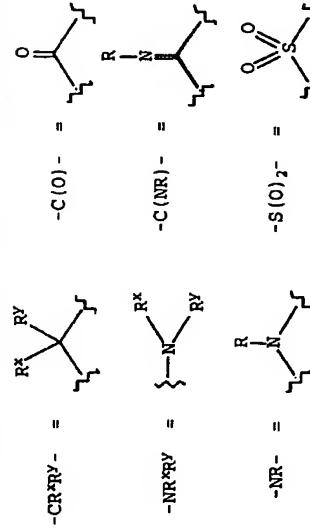
Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethyisilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-tri-silyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group.

Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyldimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzyloxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a

suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

The symbols used above have the following meanings:



Procedures for preparing the compounds of this invention are set forth below. It should be noted that the general procedures are shown as it relates to preparation of compounds having unspecified stereochemistry. However, such procedures are generally applicable to those compounds of a specific stereochemistry, e.g., where the stereochemistry about a group is (S) or (R). In addition, the compounds having one stereochemistry (e.g., (R)) can often be utilized to produce those having opposite stereochemistry (i.e., (S)) using well-known methods, for example, by inversion.

Preparation of Compounds of Formula I

The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedures. Hetero-aromatic Nitrogen Compounds: Pyrroles and Pyridines: Schofield, Kenneth; Plenum Press, New York, NY; (1967) and Advances in Nitrogen Heterocycles: JAI Press, Greenwich, CN; (1995) describe procedures and references that may be useful in preparing compounds of the present invention.

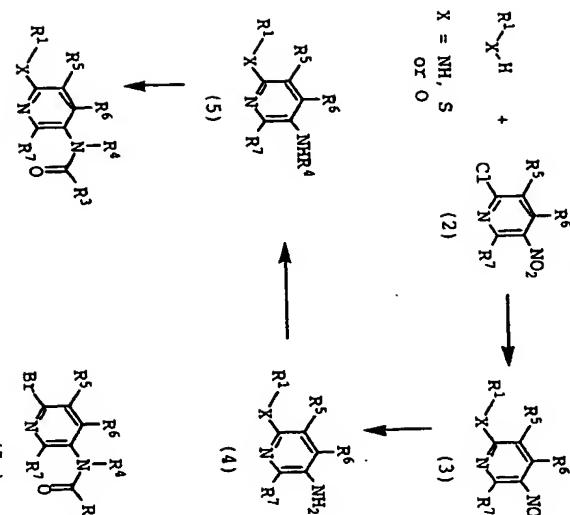
2-Halo-5-nitro-pyridine analogs (2) can be treated with the appropriate amine, alcohol, phenol, or thiol ($\text{R}'\text{X-H}$) in the presence of base or $\text{Cu}(\text{I})$ in an appropriate solvent, such as THF, DMF, DME, DMSO and the like, at a temperature from -20°C to 120°C to form 2-substituted-5-nitropyridines (3) (Scheme 1). Reduction of the nitro group can be performed by treatment of (3) with hydrogen gas in the presence of palladium on carbon or Raney nickel, or alternatively, by treatment with SnCl_4 in an alcoholic solvent and in the presence or absence of HCl to obtain 2-substituted-5-aminopyridines (4). The aminopyridines (4) may be alkylated using alkylhalides and an appropriate base or by reductive alkylation employing the appropriate aldehyde or ketone in the presence of a reducing agent, such as sodium triacetoxy borohydride, borane-THF and the like, to form the substituted aminopyridines (5). Either (4) or (5) may be acylated with an appropriate acid halide (e.g., $\text{R}'\text{C}(\text{O})\text{Cl}$ or $\text{R}'\text{C}(\text{O})\text{Br}$) in the presence of a base, such as pyridine, DMAP and the like, or alternatively may be acylated with an anhydride, either mixed or symmetrical, or alternatively may be acylated by treatment with the appropriate acid ($\text{R}'\text{CO}_2\text{H}$) in the presence of a coupling agent such as a carbodiimide reagent to form the final product (1). Alternatively, substituted 2-bromo-5-nitropyridine analogs may be reduced to, substituted 2-

35

bromo-5-aminopyridine analogs by the action of SnBr_4 in methanolic solvent. Subsequent acylation with an appropriate activated ester (i.e.: $\text{R}'\text{CO}_2\text{H}$ in the presence of diisopropylcarbodiimide in methylene chloride as solvent) produces 2-bromopyridine-5-carboxamide compounds of structure (5a). Coupling of (5a) with an appropriate phenol in the presence of $\text{Cu}(\text{Ac})_2$ and K_2CO_3 in DMF at 140°C provides compounds of formula (1) where $\text{X} = \text{O}$.

10

SCHEME I



6-Substituted-2-halo-5-nitro-pyridine analogs (6) may be prepared from 2,6-dichloro-5-nitropyridine

according to the methods outlined in Scheme II. Treatment with one equivalent of an appropriate nucleophile or R' or a precursor thereof (such as, HO⁻,

RO⁻, ACS, NC⁻, RS⁻ and the like) provides (6).

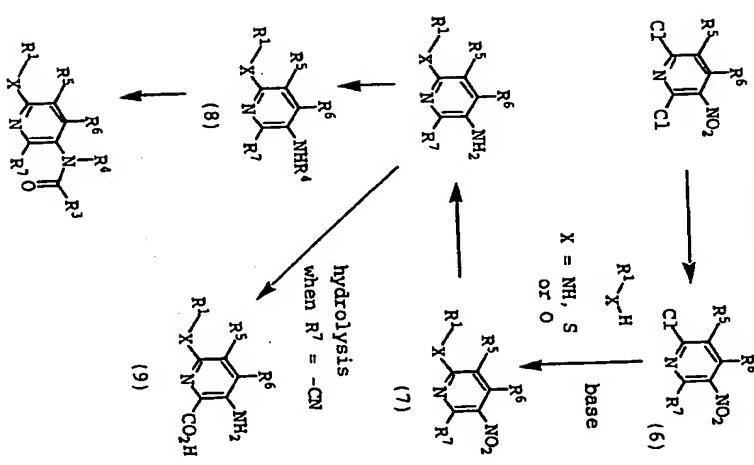
Subsequent reaction to form (7) (treatment with R'-X-H

36

in the presence of base or $\text{Cu}(\text{II})$) in an appropriate solvent, such as THF, DMF, DME, DMSO and the like, at a temperature from -20°C to 120°C) and (8) (reduction of the nitro group and substitution with R') is as described in Scheme I (cf. Colbry, N.L. et al.; J. Heterocyclic Chem., 21: 1521-1525 (1984); Matsumoto, Jun-ichi, et al.; J. Heterocyclic Chem., 21: 673-679 (1984)). (8) may be reacted with an acid halide or an activated

10

SCHEME II



ester as shown in Scheme I to provide compounds of formula (1). Where R' = CN, compounds of formula (8)

37

may be hydrolyzed to acids ($R' = CO_2H$) of formula (9) using acidic media such as HBr and the like. Utilizing the appropriate N-protecting groups, acids of formula (9) may be transformed into esters, amides and alcohols. Compounds of formula (9) and derivatives described above may be reacted with an acid halide or an activated ester as shown in Scheme I to provide compounds of formula (1). Compounds of formula (8), where $R' = -CN$, may be reduced to the primary amine ($R' = -CH_2NH_2$) using reagents such as BH₃ or hydrogen gas in the presence of palladium on carbon or Raney nickel. Subsequent manipulation and reaction of the primary amine may be performed in the presence of the pyridine-5-amine substituent due to its greater reactivity.

Specifically, compounds of formula (8) where $R' = -CH_2NH_2$, may be alkylated by treatment with an appropriate aldehyde or ketone in the presence of a reducing agent, such as sodium triacetoxy borohydride, or may be acylated by treatment with an appropriate activated ester, chloroformate, isocyanate and the like, or may be sulfonylated by treatment with an appropriate sulfonyl halide. Alternatively, substituted 3-aminopyridine intermediates may be prepared from the corresponding nicotinamide compound using Hofmann's reaction.

When R' and/or R'' is an alkyl group, such as methyl, in compound (7), containing the appropriate protecting groups or avoiding the presence of base sensitive groups, can be treated with strong base such as NaH₄, PhLi, NaH or the like at temperatures from -78°C to 22°C then treated with electrophiles, such as alkyl halides, aldehydes, ketones and the like (cf. Fuert, Feustel; CHEMTECH; 10: 693-699 (1958); Nishigaki, S. et al.; Chem. Pharm. Bull.; 17: 1827-1831 (1969); Kaiser, Edwin M.; Tetrahedron; 39: 2055-2064 (1983)). Alternatively, the alkyl group may be halogenated and the haloalkyl group may be reacted with a nucleophile, such as an amino group, alkoxy, alkylthiol and the like.

38

6-Chloronicotinoyl chloride analogs (10) are treated with the appropriate amine ($R'R'NH$) in the presence of base in an appropriate solvent, such as dichloromethane, acetonitrile, DMF, THF and the like, at a temperature from -20°C to 120°C to form nicotinamides (11) as shown in Scheme III. Alternatively, 6-chloronicotinic acid analogs (12) may be coupled with the appropriate amine via an anhydride, either mixed or symmetrical, or alternatively by treatment with the appropriate amine in the presence of a coupling agent such as a carbodiimide reagent to form the amide (11). 6-Chloronicotinamide analogs (11) are treated with the appropriate $R'X-H$ in the presence of absence of base, or Cu(I) in an appropriate solvent, such as pyridine, ethylene glycol, DMF, DMSO and the like, at a temperature from -20°C to 180°C to form the final product (13).

5

10

15

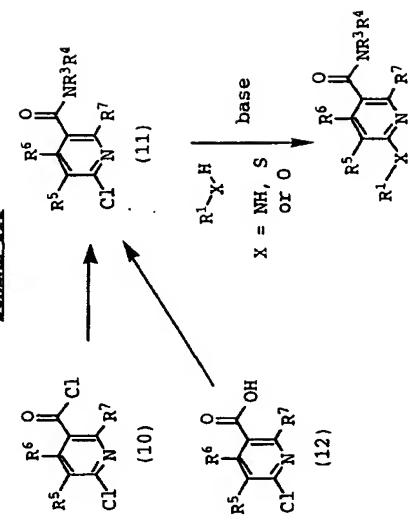
20

25

30

35

SCHEME III



20

Substituted halopyridines may be readily prepared from the corresponding pyridones using phosphorus oxychloride or pentachloride.

Amines of formula $\text{NHR}'\text{R}''$ and $\text{NHR}'\text{R}'''$ are commercially available or can be readily prepared by those skilled in the art from commercially available starting materials.

For example, an amide, nitro or cyano group can be

5 reduced under reducing conditions, such as in the

presence of a reducing agent like lithium aluminum hydride and the like, to form the corresponding amine.

Alkylation and acylation of amino groups are well known in the art. Chiral and achiral substituted amines can

10 be prepared from chiral amino acids and amino acid

amides (for example, alkyl, aryl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and the like) using methods well known in the art, such as H. Brunner, P. Hankofer, U. Holzinger, B. Treitinger

15 and H. Schoenengerger, Eur. J. Med. Chem. 25, 35-44, 1990; M. Preiburger and R. B. Hasbrouck, J. Am. Chem. Soc. 82, 696-698, 1960; Dornow and Fust, Chem. Ber. 87, 984, 1954; M. Kojima and J. Fujita, Bull. Chem. Soc. Jpn. 55, 1454-1459, 1982; W. Wheeler and D. O'Bannon, 20 Journal of Labelled Compounds and Radiopharmaceuticals XXXI, 306, 1992; and S. Davies, N. Garrido, O. Ichihara and I. Walters, J. Chem. Soc., Chem. Commun. 1153, 1993.

Alkyl sulfonic acids, aryl sulfonic acids,

heterocyclyl sulfonic acids, heteroaryl sulfonic acids, alkylmercaptans, arylmercaptans, heterocyclmercaptans,

heteroarylmercaptans, alkylhalides, arylhalides, heterocyclylhalides, heteroarylhalides, and the like are

commercially available or can be readily prepared from commercially available or can be readily prepared from starting materials commercially available using standard methods well known in the art.

30 Thioether derivatives can be converted into the corresponding sulfone or sulfoxide by oxidizing the thioether derivative with a suitable oxidation agent in a suitable solvent. Suitable oxidation agents include, for example, hydrogen peroxide, sodium meta-perborate, oxone (potassium peroxy monosulfate), meta-chloroperoxybenzoic acid, periodic acid and the like,

including mixtures thereof. Suitable solvents include acetic acid (for sodium meta-perborate) and, for other peracids, ethers such as THF and dioxane, and acetonitrile, DMF and the like, including mixtures

5 thereof.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this

occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to

10 alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily prepared from known starting materials.

20 Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of 35 Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for

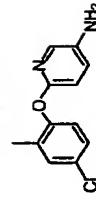
41

example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxymethyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bunggaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The following Examples illustrate the preparation of compounds of the present invention and intermediates useful in preparing the compounds of the present invention.

25

Example 1



	Example 2	Table 1
5	Step A: 2-(4-Chloro-2-methyl-phenoxy)-5-nitropyridine was dissolved in tetrahydrofuran (2.1 mL) and the solution was treated with sodium hydride (60% dispersed in mineral oil, 31 mg, 0.78 mmol). After stirring for 30	MS (m/z)
10	minutes at 22°C, 2-chloro-5-nitropyridine (101 mg, 0.64 mmol) was added and the reaction mixture was heated to reflux for 1 hour. The solution was cooled to ambient temperature, quenched with saturated aqueous NH ₄ Cl and concentrated <i>in vacuo</i> . The residue was redissolved in ethyl acetate then washed 2x with saturated NaHCO ₃ , saturated NaCl, dried over anhydrous Na ₂ SO ₄ , and concentrated <i>in vacuo</i> .	2- (4-Chloro-2-methyl-phenoxy)-5-amino-pyridine 2- (4-Chloro-2-methyl-phenoxy)-5-nitropyridine (203 mg, 0.77 mmol) was dissolved in 95% ethanol (3 mL) and treated with 20% palladium hydroxide on carbon (50 mg). The reaction mixture was shaken in a hydrogen atmosphere (40 psi) for 1 hour. The solution was filtered through celite and concentrated <i>in vacuo</i> . MS (m/z): 234/236 (M ⁺); C ₁₄ H ₁₁ N ₂ OCl requires 234.7.
15	Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The following Examples illustrate the preparation of compounds of the present invention and intermediates useful in preparing the compounds of the present invention.	Example 2 The compounds listed in Table 1 were prepared from 2-chloro-5-nitropyridine and the appropriate alcohol, amine or thiol in the same manner as 2-(4-Chloro-2-methyl-phenoxy)-5-amino-pyridine was prepared.
20	20 Examples illustrate the preparation of compounds of the present invention and intermediates useful in preparing the compounds of the present invention.	Step B: 2-(4-Chloro-2-methyl-phenoxy)-5-amino-pyridine 2- (4-Chloro-2,6-dimethylphenoxy)-5-amino-pyridine 2- (4-Chloro-2-methylphenoxy)-5-amino-pyridine 2- (4-Chloro-2-methylphenoxy)-5-nitropyridine (201 mg, 0.71 mmol) was dissolved in tetrahydrofuran (2.1 mL) and the solution was treated with sodium hydride (60% dispersed in mineral oil, 31 mg, 0.78 mmol). After stirring for 30
25	minutes at 22°C, 2-chloro-5-nitropyridine (101 mg, 0.64 mmol) was added and the reaction mixture was heated to reflux for 1 hour. The solution was cooled to ambient temperature, quenched with saturated aqueous NH ₄ Cl and concentrated <i>in vacuo</i> . The residue was redissolved in ethyl acetate then washed 2x with saturated NaHCO ₃ , saturated NaCl, dried over anhydrous Na ₂ SO ₄ , and concentrated <i>in vacuo</i> .	2- (4-Chloro-2-methyl-phenoxy)-5-amino-pyridine 2- (4-Chloro-2-methyl-phenoxy)-5-nitropyridine (201 mg, 0.77 mmol) was dissolved in 95% ethanol (3 mL) and treated with 20% palladium hydroxide on carbon (50 mg). The reaction mixture was shaken in a hydrogen atmosphere (40 psi) for 1 hour. The solution was filtered through celite and concentrated <i>in vacuo</i> . MS (m/z): 234/236 (M ⁺); C ₁₄ H ₁₁ N ₂ OCl requires 234.7.
30	Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The following Examples illustrate the preparation of compounds of the present invention and intermediates useful in preparing the compounds of the present invention.	Step A: 2-(4-Chloro-2-methyl-phenoxy)-5-nitropyridine 4-Chloro-2-methylphenol (101 mg, 0.71 mmol) was dissolved in tetrahydrofuran (2.1 mL) and the solution was treated with sodium hydride (60% dispersed in mineral oil, 31 mg, 0.78 mmol). After stirring for 30
35	minutes at 22°C, 2-chloro-5-nitropyridine (101 mg, 0.64 mmol) was added and the reaction mixture was heated to reflux for 1 hour. The solution was cooled to ambient temperature, quenched with saturated aqueous NH ₄ Cl and concentrated <i>in vacuo</i> . The residue was redissolved in ethyl acetate then washed 2x with saturated NaHCO ₃ , saturated NaCl, dried over anhydrous Na ₂ SO ₄ , and concentrated <i>in vacuo</i> .	2- (4-Chloro-2-methyl-phenoxy)-5-amino-pyridine 2- (4-Chloro-2-methyl-phenoxy)-5-nitropyridine (201 mg, 0.77 mmol) was dissolved in 95% ethanol (3 mL) and treated with 20% palladium hydroxide on carbon (50 mg). The reaction mixture was shaken in a hydrogen atmosphere (40 psi) for 1 hour. The solution was filtered through celite and concentrated <i>in vacuo</i> . MS (m/z): 234/236 (M ⁺); C ₁₄ H ₁₁ N ₂ OCl requires 234.7.

Preparation of 2-(4-Chloro-2-methyl-phenoxy)-5-amino-pyridine

2-(Cyclohexyloxy)-5-amino-pyridine	192
2-(2-Methylphenoxy)-5-amino-pyridine	200
2-(2,4-Dimethylphenoxy)-5-amino-pyridine	214
2-(4-Chlorophenoxy)-5-amino-pyridine	222
2-(Phenoxy)-5-amino-pyridine	186
2-(2-Methylcyclohexyloxy)-5-amino-pyridine	205
2-(Cyclohexyloxy)-5-amino-pyridine	191
2-(2-Methylanilino)-5-amino-pyridine	199
2-(4-Chloro-2-methylanilino)-5-amino-pyridine	233
2-(2,4-Dimethylanilino)-5-amino-pyridine	212
2-(4-Chloro-2-methylthiophenoxy)-5-amino-pyridine	251

pyridine
5 (15.8 g, 20.8 mmol) was dissolved in 95% ethanol (150 mL) and treated with 20% palladium hydroxide on carbon (350 mg). The reaction mixture was shaken in a hydrogen atmosphere (40 psi) for 1 hour. The solution was filtered through celite and concentrated in vacuo

10 followed by chromatography on SiO, using 1:1 ethyl acetate / hexanes as eluant. MS (*m/z*): 248/250 ($M+H$)⁺; C₉H₁₁N₂OCl requires 248.7.

Example 4
15 The compounds listed in Table 2 were prepared from substituted 2-chloro-5-nitropyridine and 4-chloro-2-methylphenol in the same manner as 2-(4-Chloro-2-methylphenoxy)-3-methyl-5-amino-pyridine was prepared.

Table 2

MS
(*m/z*)

2-(4-Chloro-2-methyl-phenoxy)-4-methyl-5-amino-

pyridine

6-(4-Chloro-2-methyl-phenoxy)-2-methyl-3-amino-

pyridine

6-(4-Chloro-2-methyl-phenoxy)-2,3-diamino-

pyridine

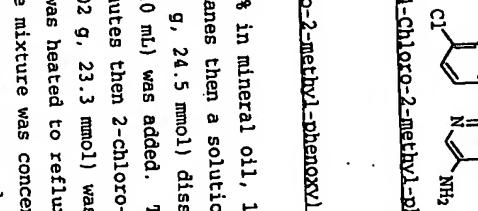
Example 5

15 **Step A: 2-(4-Chloro-2-methoxy-3-methyl-5-amino-pyridine**

Sodium hydride (60% in mineral oil, 1.08 g, 27 mmol) was washed 3x with hexanes then a solution of 4-chloro-2-methylphenol (3.50 g, 24.5 mmol) dissolved in tetrahydrofuran (40 mL) was added. The solution was stirred for 20 minutes then 2-chloro-3-methyl-5-nitropyridine (4.02 g, 23.3 mmol) was added and the reaction mixture was heated to reflux for 3 hours.

After cooling, the mixture was concentrated in vacuo, then dissolved in ethyl acetate and washed with water, 3x with saturated NaHCO₃ and saturated NaCl then dried over Na₂SO₄ and concentrated in vacuo.

25 **Preparation of N-(2-(4-Chloro-2-methoxy-3-methyl-5-**



Preparation of 2-(4-Chloro-2-methoxy-3-methyl-5-

5-amino-pyridine

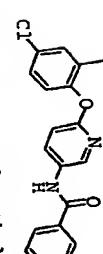
Step A: 2-(4-Chloro-2-methoxy-3-methyl-5-

nitropyridine

Sodium hydride (60% in mineral oil, 1.08 g, 27 mmol) was washed 3x with hexanes then a solution of 4-chloro-2-methylphenol (3.50 g, 24.5 mmol) dissolved in tetrahydrofuran (40 mL) was added. The solution was stirred for 20 minutes then 2-chloro-3-methyl-5-nitropyridine (4.02 g, 23.3 mmol) was added and the reaction mixture was heated to reflux for 3 hours.

After cooling, the mixture was concentrated in vacuo, then dissolved in ethyl acetate and washed with water, 3x with saturated NaHCO₃ and saturated NaCl then dried over Na₂SO₄ and concentrated in vacuo.

25 **Preparation of N-(2-(4-Chloro-2-methoxy-3-methyl-5-**



2-(4-Chloro-2-methyl-phenoxo)-5-aminopyridine (211 mg, 0.90 mmol) was dissolved in methylene chloride (2.7 mL) then treated with triethylamine (0.19 mL, 1.35 mmol) followed by benzoyl chloride (0.13 mL, 1.12 mmol). The reaction mixture was stirred for 3 hours at 22°C then saturated aqueous NaHCO_3 was added and the mixture was stirred for another hour. The organic layer was separated and washed 2x with 6% aqueous NaHCO_3 , dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using 1:1 ethyl acetate / hexane as eluent. The product was recovered as a white solid. MS (m/z): 338/340 (M+H)⁺; $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2\text{Cl}$ requires 338.8.

Example 6
The compounds listed in Table 3 were prepared from substituted 5-aminopyridine compounds and the appropriate acid chloride in the same manner as N-(2-(4-Chloro-2-methyl-phenoxy)-pyridin-5-yl)-benzamide was prepared.

Table 3

MS (m/z)			
384	2-(4-Chloro-2-methyl-phenoxy)-5-((2-nitrophenyl)carbonylamino)pyridine	397	2-(4-Chloro-2-methyl-phenoxy)-5-((2-acetoxyphenyl)carbonylamino)pyridine
340	2-(4-Chloro-2-methyl-phenoxy)-5-((2-dichlorophenyl)carbonylamino)pyridine	408	2-(4-Chloro-2, 6-dimethylphenoxy)-5-((2, 6-dichlorophenyl)carbonylamino)pyridine
340	2-(4-Chloro-2, 6-dimethylphenoxy)-5-((2, 6-dimethylphenyl)carbonylamino)pyridine	369	2-(2-methyl-pyridin-3-yloxy)-5-((2, 6-dichlorophenyl)carbonylamino)pyridine
340	2-(4-Chloro-2, 6-dimethylphenoxy)-5-((2, 6-dimethylphenyl)carbonylamino)pyridine	409	2-(2-methyl-pyridin-3-yloxy)-5-((2, 6-dimethylphenyl)carbonylamino)pyridine
389	2-(2-methyl-pyridin-3-yloxy)-5-((2-methylphenyl)carbonylamino)pyridine		

2-(4-fluoro-2-methylphenoxy)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	391	2-(2-methylphenoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	332
2-(4-fluoro-2-methylphenoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	350	2-(2-methylphenoxy)-5-((2-methylphenyl)carbonylamino)pyridine	339
2-(4-fluoro-2-methylphenoxy)-5-((2-methylphenyl)carbonylamino)pyridine	336	2-(2-methylphenoxy)-5-((2-methylphenyl)carbonylamino)pyridine	318
2-(4-fluoro-2-methylphenoxy)-5-((2-methylphenyl)carbonylamino)pyridine	390	2-(2,4-dimethylphenoxy)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	387
2-(4-fluoro-2-methylphenoxy)-5-((2-methylphenyl)carbonylamino)pyridine	340	2-(2,4-dimethylphenoxy)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	346
2-(2-isopropylphenoxy)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	401	2-(2,4-dimethylphenoxy)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	353
2-(2-isopropylphenoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	346	2-(2,4-dimethylphenoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	332
2-(2-isopropylphenoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	409	2-(4-chlorophenoxy)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	394
2-(1-naphthoxy)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	368	2-(4-chlorophenoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	353
2-(1-naphthoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	354	2-(2-methylcyclohexylamino)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	378
2-(1-naphthoxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	365	2-(2-methylcyclohexylamino)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	323
2-(cyclohexyloxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	324	2-(cyclohexylamino)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	364
2-(cyclohexyloxy)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	331	2-(cyclohexylamino)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	323
2-(cyclohexyloxy)-5-((2-chlorophenyl)carbonylamino)pyridine	310	2-(cyclohexylamino)-5-((2-methylphenyl)carbonylamino)pyridine	309
2-(cyclohexyloxy)-5-((2-methylphenyl)carbonylamino)pyridine	373	2-(2-methylanilino)-5-((2,6-dichlorophenyl)carbonylamino)pyridine	372
2-(2-methylphenyl)carbonylamino)pyridine		2-(2-methylanilino)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	331

2-(2-methylanilino)-5-(2-methylphenyl)carbonylamino)pyridine

317

49

		Table 4	MS (m/z)
2-(4-chloro-2-methylanilino)-5-(2,6-dichlorophenyl)carbonylamino)pyridine	407	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-dichlorophenyl)carbonylamino)-3-methyl-pyridine	422
2-(4-chloro-2-methylanilino)-5-(2,6-dimethylphenyl)carbonylamino)pyridine	366	2-(4-Chloro-2-methyl-phenoxy)-5-((2-chlorophenyl)carbonylamino)-3-methyl-pyridine	387
2-(4-chloro-2-methylanilino)-5-(2-methylphenyl)carbonylamino)pyridine	352	2-(4-Chloro-2-methyl-phenoxy)-5-((2-methylphenyl)carbonylamino)-3-methyl-pyridine	367
2-(2,4-dimethylanilino)-5-(2,6-dichlorophenyl)carbonylamino)pyridine	386	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-dimethylphenyl)carbonylamino)-3-methyl-pyridine	332
2-(2,4-dimethylanilino)-5-(2,6-dimethylphenyl)carbonylamino)pyridine	345	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-dimethylphenyl)carbonylamino)-3-methyl-pyridine	422
2-(2,4-dimethylanilino)-5-(2-methylphenyl)carbonylamino)pyridine	331	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-trifluoromethylphenyl)carbonylamino)-4-methyl-pyridine	439
2-(2,4-dimethylanilino)-5-(2-methylphenyl)carbonylamino)pyridine	352	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-trifluoromethylphenyl)carbonylamino)-4-methyl-pyridine	479
2-(2,4-dimethylanilino)-5-(2-chlorophenyl)carbonylamino)pyridine	335	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-triisopropylphenyl)carbonylamino)-4-methyl-pyridine	479
2-(2,4-dimethylanilino)-5-(2-fluorophenyl)carbonylamino)pyridine	424	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-methylphenyl)carbonylamino)-6-methyl-pyridine	367
2-(4-chloro-2-methyl-thiophenyl)carbonylamino)pyridine	424	2-(4-Chloro-2-methyl-phenoxy)-5-((2-chlorophenyl)carbonylamino)-6-methyl-pyridine	387
2-(4-chloro-2-methyl-thiophenyl)carbonylamino)pyridine	383	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-dimethylphenyl)carbonylamino)-6-methyl-pyridine	422
2-(4-chloro-2-methyl-thiophenyl)carbonylamino)pyridine	369	2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-dichlorophenyl)carbonylamino)-6-methyl-pyridine	423
		2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-dichlorophenyl)carbonylamino)-6-amino-pyridine	388
		2-(4-Chloro-2-methyl-phenoxy)-5-((2-chlorophenyl)carbonylamino)-6-amino-pyridine	382
		2-(4-Chloro-2-methyl-phenoxy)-5-((2,6-dimethylphenyl)carbonylamino)-6-amino-pyridine	

Example 7

The compounds listed in Table 4 were prepared from substituted 5-aminopyridine compounds and the appropriate acid chloride in the same manner as N-(2-(4-Chloro-2-methyl-phenoxy)-pyridin-5-yl)-benzamide was prepared.

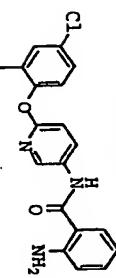
51

2-(4-Chloro-2-methyl-phenoxyl)-5-((2-methylphenyl)carbonylamino)-6-amino-pyridine

368

with water, 2x saturated NaHCO_3 , saturated NaCl , dried over Na_2SO_4 and concentrated in vacuo. MS (m/z): 354/356 ($\text{M}+\text{H}^+$); $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2\text{Cl}$ requires 354.8.

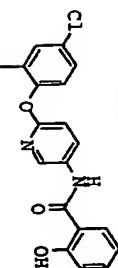
Example 8



5 Preparation of 2-Amino-N-(6-(4-chloro-2-methyl-phenoxyl)-pyridin-3-yl)-benzamide

10 **N-(6-(4-chloro-2-methyl-phenoxyl)-pyridin-3-yl)-2-nitrobenzamide** (301 mg, 0.7 mmol) was dissolved in 95% ethanol (4 mL) and treated with 20% palladium hydroxide on carbon (Pearlman's catalyst, 50 mg) and subjected to a hydrogen atmosphere (40 psi) for 2 hours. The catalyst was removed by filtration and the solvents were removed in vacuo. The product was purified by chromatography on SiO_2 using 1:1 ethyl acetate / hexanes as eluent. MS (m/z): 353/355 ($\text{M}+\text{H}^+$); $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2\text{Cl}$ requires 353.8.

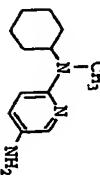
Example 9



20 Preparation of N-(6-(4-chloro-2-methyl-phenoxyl)-pyridin-3-yl)-2-hydroxy-benzamide

15 **Acetic acid 2-(6-(4-chloro-2-methyl-phenoxyl)-pyridin-3-ylcarbamoyl)-phenyl ester** (304 mg, 0.77 mmol) dissolved in tetrahydrofuran (3.8 mL) was treated with an aqueous lithium hydroxide solution (1.0 M, 3.8 mL, 3.8 mmol). The solution was stirred for 30 minutes at 22°C then quenched with aqueous saturated NH_4Cl . The mixture was diluted with ethyl acetate then the organics were washed

Example 10



5 Preparation of 2-(N-Cyclohexyl-N-methylamino)-5-nitro-pyridine

10 **Step A: 2-(Cyclohexylamino)-5-nitro-pyridine**
Sodium hydride (60% dispersion in mineral oil, 1.99 g, 49.8 mmol) was washed 3x with hexanes then a solution of cyclohexylamine (3.8 mL, 33.2 mmol) dissolved in tetrahydrofuran (50 mL) was added. After stirring for 30 minutes at 22 °C, 2-chloro-5-nitropyridine (5.00 g, 31.5 mmol) was added and the reaction mixture was heated to reflux for 3 hours. The solution was cooled to ambient temperature, quenched with saturated aqueous NH_4Cl and concentrated in vacuo. The residue was redissolved in ethyl acetate then washed 2x with saturated NaHCO_3 , saturated NaCl , dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The product was recovered as a brown oil.

20 **Step B: 2-(N-Cyclohexyl-N-methylamino)-5-nitro-pyridine**
Sodium hydride (60% dispersion in mineral oil, 0.38 g, 9.48 mmol) was washed 3x with hexanes then a solution of 2-cyclohexylamino-5-nitropyridine (1.88 g, 8.5 mmol) dissolved in dimethylformamide (20 mL) was added. After stirring for 30 minutes at 22°C, the reaction mixture was cooled to 0°C and methyl iodide (0.55 mL, 8.9 mmol) was added. The solution was stirred for 1.5 hours at 0°C followed by quenching with saturated aqueous NH_4Cl . The reaction mixture was diluted with ethyl acetate and

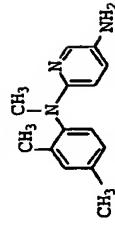
53

extracted 5x with water (200 mL), saturated NaCl, dried over Na₂SO₄ and concentrated in vacuo oil was chromatographed on SiO₂ using 2:1 hexanes / ethyl acetate as eluent.

5

Step C: 2-(N-Cyclohexyl-N-methylamino)-5-amino-pyridine
 Cyclohexyl-methyl-(5-nitro-pyridin-2-yl)-amine (1.72 g, 7.3 mmol) was dissolved in ethanol (80 mL) and treated with 20% palladium hydroxide on carbon (Pearlman's catalyst, 0.5 g) and the mixture was shaken under a hydrogen atmosphere (50 psi) for 6 hours. The catalyst was removed by filtration through celite then the filtrate was concentrated in vacuo and the resultant oil was chromatographed on SiO₂ using 1:1 ethyl acetate / hexanes as eluent. MS (m/z): 206 (M+H)⁺; C₁₁H₁₄N, requires 205.3.

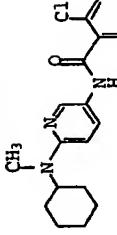
15

Example 11

Preparation of 2-(N-(2,4-dimethylphenyl)-N-methylamino)-5-amino-pyridine

2-(N-(2,4-dimethylphenyl)-N-methylamino)-5-amino-pyridine was prepared from 1-amino-2,4-dimethylbenzene and 2-chloro-5-nitropyridine in the same manner as 2-(N-methylamino)-5-amino-pyridine was prepared.

25

Example 12

Preparation of 2,6-Dichloro-N-(2-(N'-cyclohexyl-N-methylamino)-pyridin-5-yl)-benzamide

30

54

2-(N-Cyclohexyl-N-methylamino)-5-amino-pyridine (26 mg, 0.13 mmol) dissolved in methylene chloride (0.25 mL) was treated with triethylamine (0.026 mL, 0.18 mmol) followed by a solution of 2,6-dichlorobenzoyl chloride (0.15 mL, 0.15 mmol) dissolved in methylene chloride (0.15 mL). The reaction mixture was shaken at 22°C for 18 hours followed by quenching with saturated aqueous NH₄Cl and stirring for an additional 5 hours. The organic layer was separated and dried over Na₂SO₄, then concentrated in vacuo. The crude product was purified by chromatography on SiO₂ using 1:1 ethyl acetate / hexane as eluent. MS (m/z): 378/380 (M+H)⁺; C₁₈H₁₈N₂OCl

5

10

15

Example 13

The compounds listed in Table 5 were prepared from substituted 5-aminopyridine compounds and the appropriate acid chloride in the same manner as 2,6-Dichloro-N-(2-(N'-cyclohexyl-N'-methylamino)-pyridin-5-yl)-benzamide was prepared.

Table 5

	MS (m/z)
2-(N-Cyclohexyl-N-methylamino)-5-(1,2,6-dichlorophenyl)pyridine	378
2-(N-Cyclohexyl-N-methylamino)-5-(1,2-chlorophenyl)pyridine	344
2-(N-Cyclohexyl-N-methylamino)-5-((2-methylphenyl)carbonylamino)pyridine	323
2-(N-Cyclohexyl-N-methylamino)-5-((2,6-dimethylphenyl)carbonylamino)pyridine	337
2-(2,4-dimethylphenyl)-5-(1,2,6-dimethylphenyl)pyridine	359

2-(2,4-dimethylphenyl)-5-(1-(2-methylphenyl)carbonylamino)pyridine

345

2-(2,4-dimethylphenyl)-5-(1-(2-chlorophenyl)carbonylamino)pyridine

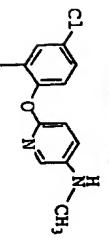
366

2-(2,4-dimethylphenyl)-5-(1-(2-fluorophenyl)carbonylamino)pyridine

349

2-(2,4-dimethylphenyl)-5-(1-(2-dichlorophenyl)carbonylamino)pyridine

400



Example 14

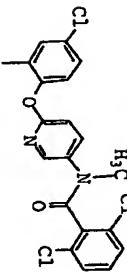
Preparation of 2-(4-Chloro-2-methyl-phenoxy)-5-(N-methylaminopyridine)

2-(4-Chloro-2-methyl-phenoxy)-5-aminopyridine (2.15 g, 9.16 mmol) was combined with powdered sodium hydroxide (1.46 g, 36.6 mmol), potassium carbonate (1.27 g, 9.16 mmol), tetrabutyl ammonium bromide (60 mg, 0.18 mmol) and toluene (10 mL) was stirred for 1 hour at 35°C. A

solution of dimethyl sulfate (0.91 mL, 9.6 mmol) dissolved in toluene (5 mL) was added slowly. The mixture was heated at 35°C for 20 hours. After cooling, the solids were removed by filtration and the solvent was concentrated in vacuo. The desired material was purified by chromatography on SiO₂ using 1:1 ethyl acetate / hexane as eluent. MS (m/z): 422/424 (M+H)⁺; C₁₆H₁₄N₂O₂Cl₂ requires 422.

20

Example 15



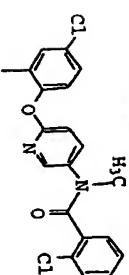
Preparation of 2-(4-chlorophenoxy)-N-(6-(4-chloro-2-methylphenyl)benzyl)benzamide

2-(4-Chloro-2-methyl-phenoxy)-5-(N-methylaminopyridine) (32 mg, 0.13 mmol) dissolved in methylene chloride (0.25 mL) was treated with triethylamine (0.026 mL, 0.18 mmol) followed by a solution of 2,6-dichlorobenzoyl chloride (0.15 mL) in methylene chloride (0.15 mL). The reaction mixture was shaken at 22°C for 18

hours followed by quenching with saturated aqueous NH₄Cl and stirring for an additional 5 hours. The organic layer was separated and dried over Na₂SO₄, then concentrated in vacuo. The crude product was purified by chromatography on SiO₂ using 1:1 ethyl acetate / hexane as eluent. MS (m/z): 422/424 (M+H)⁺; C₁₆H₁₄N₂O₂Cl₂ requires 422.

20

Example 16

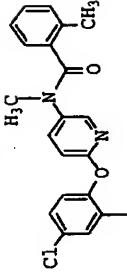


Preparation of 2-Chloro-N-(6-(4-chloro-2-methylphenyl)benzyl)benzamide

2-Chloro-N-(6-(4-chloro-2-methylphenyl)benzyl)benzamide was prepared from 2-(4-Chloro-2-methyl-phenyl)benzyl chloride in the same manner as 2,6-dichloro-N-(6-(4-chloro-2-methyl-phenyl)-pyridin-3-yl)-N-methyl-benzamide was prepared.

30

57

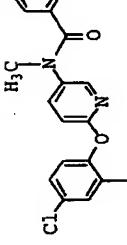
Example 17Preparation of 2-Methyl-1-N-(6-(4-chloro-2-methylphenoxy)-2-methyl-phenoxyl)-pyridin-3-yl-N-methylbenzamide

5 2-Methyl-1-N-(6-(4-chloro-2-methylphenoxy)-2-methyl-phenoxyl)-pyridin-3-yl-N-methylbenzamide was prepared from 2-(4-chloro-2-methylphenoxy)-5-(N-methylamino)pyridine and 2-methylbenzoyl chloride in the same manner as 2,6-Dichloro-N-(6-(4-chloro-2-methylphenoxy)-2-methyl-phenoxyl)-N-methylbenzamide was prepared.

58

Table 6

	R ¹ X	R ³	MS (m/z)
4-chloro-2-methylphenoxy	4-biphenyl		415
4-chloro-2-methylphenoxy	3,4-dimethoxyphenyl		319
4-chloro-2-methylphenoxy	2-(trifluoromethyl)phenyl		407
4-chloro-2-methylphenoxy	2,4-difluorophenyl		375
4-chloro-2-methylphenoxy	4-cyanophenyl		364
4-chloro-2-methylphenoxy	3-(trifluoromethyl)phenyl		407
4-chloro-2-methylphenoxy	3-cyanophenyl		364
4-chloro-2-methylphenoxy	2-naphthyl		389
4-chloro-2-methylphenoxy	2-methoxyphenyl		369
4-chloro-2-methylphenoxy	4-chloro-2-methylphenyl		429
4-chloro-2-methylphenoxy	4-nitrophenyl		384
4-chloro-2-methylphenoxy	3,4-dichlorophenyl		408
4-chloro-2-methylphenoxy	5-nitrofuran-2-yl		374
4-chloro-2-methylphenoxy	3-bromophenyl		418

Example 18

General procedure for the synthesis of 2-substituted-5-acylamino-pyridines

15 A solution of the 2-substituted-5-aminopyridine (10 mmol), triethylamine (10 mmol) and an acid chloride (20 mmol) in ethanol free chloroform (250 mL) was shaken for 16 hours. The mixture was then diluted with saturated aqueous sodium hydrogen carbonate (50 mL) and dichloromethane (500 mL), and shaken for 30 min. The mixture was then filtered through anhydrous magnesium sulfate, washing with dichloromethane (250 mL).

Concentration of the filtrate under reduced pressure afforded the desired 2-substituted-5-acylaminopyridines.

16 The compounds listed in Table 6 were prepared from substituted 5-aminopyridine compounds and the appropriate acid chloride according to the general procedure above.

17 The compounds listed in Table 6 were prepared from substituted 5-aminopyridine compounds and the appropriate acid chloride according to the general procedure above.

59

60

4-chloro-2-methylphenoxy	3-pyridyl	340	4-chloro-2-methylphenoxy	1-(2-(2-methylpropyl)pyridin-3-methyl)pyrazol-5-yl	399
4-chloro-2-methylphenoxy	2-ethoxynaphth-1-yl	433	4-chloro-2-methylphenoxy	3,5-dichlorophenyl	408
4-chloro-2-methylphenoxy	2,3-dichlorophenyl	408	4-chloro-2-methylphenoxy	2-(propylthio)pyridin-3-yl	414
4-chloro-2-methylphenoxy	3-nitrophenyl	384	4-chloro-2-methylphenoxy	2-(ethylthio)pyridin-3-yl	400
4-chloro-2-methylphenoxy	6-chloropyrid-3-yl	374	4-chloro-2-methylphenoxy	3-bromopyridin-5-yl	419
4-chloro-2-methylphenoxy	4-(trifluoromethoxy)phenyl	423	4-chloro-2-methylphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	361
4-chloro-2-methylphenoxy	2-fluoro-4-(trifluoromethyl)phenyl	425	4-chloro-2-methylphenoxy	1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl	399
4-chloro-2-methylphenoxy	2-acetoxyphenyl	397	4-chloro-2-methylphenoxy	3-chlorobenzol[b]thiophen-2-yl	429
4-chloro-2-methylphenoxy	5-methylisoxazol-3-yl	344	4-chloro-2-methylphenoxy	4-chlorophenyl	373
4-chloro-2-methylphenoxy	2-(phenylthio)pyrid-3-yl	448	4-chloro-2-methylphenoxy	4-methyl-1,2,3-triazol-5-yl	420
4-chloro-2-methylphenoxy	2-(trifluoromethoxy)phenyl	423	4-chloro-2-methylphenoxy	benzo[b]thiophen-2-yl	395
4-chloro-2-methylphenoxy	1-phenyl-5-propyl-pyrazin-4-yl	447	4-chloro-2-methylphenoxy	3,4-dimethylphenyl	367
4-chloro-2-methylphenoxy	2-ethoxyphenyl	383	4-chloro-2-methylphenoxy	2-(phenoxyl)pyridin-3-yl	432
4-chloro-2-methylphenoxy	3-chlorothien-2-yl	379	4-chloro-2-methylphenoxy	2-(methylthio)pyridin-3-yl	386
4-chloro-2-methylphenoxy	3-bromothien-2-yl	424	4-chloro-2-methylphenoxy	5-methyl-3-phenylisoxazol-4-yl	420

61

4-chloro-2-methylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	442
4-chloro-2-methylphenoxy	2-chloro-6-methylpyridin-4-yl	388
4-chloro-2-methylphenoxy	3,5-dimethylisoxazol-4-yl	358
4-chloro-2-methylphenoxy	1-naphthyl	389
4-chloro-2-methylphenoxy	2-fluorophenyl	357
4-chloro-2-methylphenoxy	4-propylphenyl	381
4-chloro-2-methylphenoxy	4-(trifluoromethyl)phenyl	407
4-chloro-2-methylphenoxy	3-fluorophenyl	357
4-chloro-2-methylphenoxy	2,6-difluorophenyl	375
4-chloro-2-methylphenoxy	2-chlorophenyl	373
4-chloro-2-methylphenoxy	3-(chloromethyl)phenyl	387
4-chloro-2-methylphenoxy	4-(2-(2-methylpropyl)phenyl	395
4-chloro-2-methylphenoxy	3-chlorophenyl	373
4-chloro-2-methylphenoxy	2-nitrophenyl	388
4-chloro-2-methylphenoxy	3,5-dimethoxyphenyl	399

62

methylphenoxy	2, 4-dichlorophenyl
4-chloro-2-methylphenoxy	4-fluorophenyl
4-chloro-2-methylphenoxy	4-butylphenyl
4-chloro-2-methylphenoxy	2-methylphenyl
4-chloro-2-methylphenoxy	phenyl
4-chloro-2-methylphenoxy	4-ethylphenyl
4-chloro-2-methylphenoxy	2, 3-difluorophenyl
4-chloro-2-methylphenoxy	2, 6-dimethoxyphenyl
4-chloro-2-methylphenoxy	2, 5-difluorophenyl
4-chloro-2-methylphenoxy	4-ethoxyphenyl
4-chloro-2-methylphenoxy	2, 4, 6-trichlorophenyl
4-chloro-2-methylphenoxy	3-methylphenyl
4-chloro-2-methylphenoxy	2-fluoro-5-(trifluoromethyl)phenyl
4-chloro-2-methylphenoxy	3-methoxyphenyl
4-chloro-2-methylphenoxy	thien-2-yl

63

64

4-chloro-2-methylphenoxy	2-bromophenyl	418	1-naphthoxy	3-(trifluoromethyl)phenyl	408
4-chloro-2-methylphenoxy	4-bromophenyl	418	1-naphthoxy	3-cyanophenyl	365
4-chloro-2-methylphenoxy	(trifluoromethyl)phenyl	425	1-naphthoxy	2-naphthyl	390
4-chloro-2-methylphenoxy	3-(trifluoromethoxy)phenyl	423	1-naphthoxy	2-methoxyphenyl	370
4-chloro-2-methylphenoxy	9-fluoren-4-yl	441	1-naphthoxy	3,4,5-trimethylphenyl	430
4-chloro-2-methylphenoxy	isoxazol-5-yl	330	1-naphthoxy	4-nitrophenyl	385
4-chloro-2-methylphenoxy	benzofuroxan-5-yl	397	1-naphthoxy	3,4-dichlorophenyl	409
4-chloro-2-methylphenoxy	2-chloropyrid-3-yl	374	1-naphthoxy	5-nitrofuran-2-yl	375
4-chloro-2-methylphenoxy	3,5-difluorophenyl	375	1-naphthoxy	3-bromophenyl	419
4-chloro-2-methylphenoxy	2-(4-methylphenoxy)pyridin-3-yl	446	1-naphthoxy	3-pyridyl	341
4-chloro-2-methylphenoxy	pyridin-4-yl	340	1-naphthoxy	2-ethoxynaphth-1-yl	334
4-chloro-2-methylphenoxy	anthraquinon-2-yl	469	1-naphthoxy	2,3-dichlorophenyl	409
4-chloro-2-methylphenoxy	2-iodophenyl	465	1-naphthoxy	3-nitrophenyl	385
4-chloro-2-methylphenoxy	4-biphenyl	416	1-naphthoxy	6-chloropyrid-3-yl	376
1-naphthoxy	3,4-dimethoxyphenyl	400	1-naphthoxy	2-(trifluoromethoxy)phenyl	424
1-naphthoxy	2-(trifluoromethyl)phenyl	408	1-naphthoxy	2-fluoro-4-(trifluoromethyl)phenyl	426
1-naphthoxy	2,4-difluorophenyl	376	1-naphthoxy	3-bromothiophenyl	425
1-naphthoxy	4-cyanophenyl	365	1-naphthoxy	2-acetoxyphenyl	398

WO 99/74404	65	66
3, 5-dichlorophenoxy	409	1-naphthoxy
2-(propylthio)pyridin-3-yl	415	1-naphthoxy
2-(ethylthio)pyridin-3-yl	401	1-naphthoxy
3-bromopyridin-5-yl	420	1-naphthoxy
4-methyl-1,2,3-thiadiazol-5-yl	362	1-naphthoxy
1-methyl-3-(2-(2-methylpropyl)pyrazol-5-yl)	400	1-naphthoxy
3-chlorobenzo[b]thiophen-2-yl	431	1-naphthoxy
4-chlorophenoxy	375	1-naphthoxy
4-methyl-2-phenyl-1,2,3-triazol-5-yl	421	1-naphthoxy
benz[b]thiophen-2-yl	396	1-naphthoxy
3, 4-dimethylphenyl	368	1-naphthoxy
2-(phenoxyl)pyridin-3-yl	433	1-naphthoxy
2-(methylthio)pyridin-3-yl	387	1-naphthoxy
5-methyl-3-phenylisoxazol-4-yl	421	1-naphthoxy
4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	444	1-naphthoxy
2-chloro-6-methylpyridin-4-yl	390	1-naphthoxy
3, 5-dimethylisoxazol-4-yl	359	1-naphthoxy
1-naphthoxy	390	1-naphthoxy
2-fluorophenyl	358	1-naphthoxy
4-propylphenyl	382	1-naphthoxy
4-(trifluoromethyl)phenyl	408	1-naphthoxy
3-fluorophenyl	358	3-methoxyphenyl
1-naphthoxy	370	thien-2-yl
1-naphthoxy	346	2-bromophenyl
1-naphthoxy	419	4-bromophenyl

67

68

1-naphthoxy	4-fluoro-3-(trifluoromethyl)phenyl	426	2-(2-propyl)phenoxy	2-ethoxynaphth-1-yl	426
1-naphthoxy	3-(trifluoromethoxy)phenyl	424	2-(2-propyl)phenoxy	2,3-dichlorophenyl	401
1-naphthoxy	9-fluoren-4-yl	442	2-(2-propyl)phenoxy	3-nitrophenyl	377
1-naphthoxy	isoxazol-5-yl	331	2-(2-propyl)phenoxy	6-chloropyrid-3-yl	368
1-naphthoxy	benzofuran-5-yl	398	2-(2-propyl)phenoxy	4-(trifluoromethoxy)phenyl	416
1-naphthoxy	2-chloropyrid-3-yl	376	2-(2-propyl)phenoxy	2-fluoro-4-(trifluoromethyl)phenyl	418
1-naphthoxy	3,5-difluorophenyl	376	2-(2-propyl)phenoxy	3-bromothiophenyl	417
1-naphthoxy	2-(4-methylphenoxy)pyridin-3-yl	447	2-(2-propyl)phenoxy	2-acetoxyphenyl	390
1-naphthoxy	pyridin-4-yl	341	2-(2-propyl)phenoxy	5-methylisoxazol-3-yl	337
1-naphthoxy	anthraquinon-2-yl	470	2-(2-propyl)phenoxy	2-(phenylthio)pyrid-3-yl	442
1-naphthoxy	2-iodophenyl	466	2-(2-propyl)phenoxy	2-(trifluoromethoxy)phenyl	416
2-(2-propyl)phenoxy	4-biphenyl	408	2-(2-propyl)phenoxy	1-phenyl-5-propylpyrazin-4-yl	441
2-(2-propyl)phenoxy	3,4-dimethoxyphenyl	392	2-(2-propyl)phenoxy	2-ethoxyphenyl	376
2-(2-propyl)phenoxy	2-(trifluoromethyl)phenyl	400	2-(2-propyl)phenoxy	3-chlorothien-2-yl	373
2-(2-propyl)phenoxy	2,4-difluorophenyl	368	2-(2-propyl)phenoxy	1-(2-(2-methylpropyl)-3-methylpyrazol-5-yl	392
2-(2-propyl)phenoxy	4-cyanophenyl	357	2-(2-propyl)phenoxy	3,5-dichlorophenyl	401
2-(2-propyl)phenoxy	3-(trifluoromethyl)phenyl	400	2-(2-propyl)phenoxy	2-(propylthio)pyridin-3-yl	407
2-(2-propyl)phenoxy	3-cyanophenyl	357	2-(2-propyl)phenoxy	2-(ethylthio)pyridin-3-yl	393
2-(2-propyl)phenoxy	2-naphthyl	382	2-(2-propyl)phenoxy	3-bromopyridin-5-yl	412
2-(2-propyl)phenoxy	2-methoxyphenyl	362	2-(2-propyl)phenoxy	4-methyl-1,2,3-thiadiazol-5-yl	354
2-(2-propyl)phenoxy	3,4,5-trimethylphenyl	422	2-(2-propyl)phenoxy	1-methyl-3-(2-(2-methylpropyl)pyrazol-5-yl	392
2-(2-propyl)phenoxy	4-nitrophenyl	377	2-(2-propyl)phenoxy	3-chlorobenz[b]thiophen-2-yl	423
2-(2-propyl)phenoxy	3,4-dichlorophenyl	401	2-(2-propyl)phenoxy	4-chlorophenyl	367
2-(2-propyl)phenoxy	5-nitrofuran-2-yl	367			
2-(2-propyl)phenoxy	3-bromophenyl	411			
2-(2-propyl)phenoxy	3-pyridyl	333			

2-(2-propyl)phenoxy	4-methyl-1-2-phenyl-1,2,3-triazol-5-yl	388
2-(2-propyl)phenoxy	benzo[b]thiophen-2-yl	366
2-(2-propyl)phenoxy	3, 4-dimethylphenyl	422
2-(2-propyl)phenoxy	2-(phenoxy)pyridin-3-yl	422
2-(2-propyl)phenoxy	2-(methylthio)pyridin-3-yl	377
2-(2-propyl)phenoxy	5-methyl-1-3-phenylisoxazol-4-yl	411
2-(2-propyl)phenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	433
2-(2-propyl)phenoxy	2-chloro-6-methylpyridin-4-yl	388
2-(2-propyl)phenoxy	3,5-dimethylisoxazol-4-yl	355
2-(2-propyl)phenoxy	1-naphthyl	388
2-(2-propyl)phenoxy	2-fluorophenyl	355
2-(2-propyl)phenoxy	4-propylphenyl	377
2-(2-propyl)phenoxy	4-(trifluoromethyl)phenyl	400
2-(2-propyl)phenoxy	3-fluorophenyl	355
2-(2-propyl)phenoxy	2, 6-difluorophenyl	366
2-(2-propyl)phenoxy	2-chlorophenyl	366
2-(2-propyl)phenoxy	3-(chloromethyl)phenyl	388
2-(2-propyl)phenoxy	4-(2-(2-methyl)propyl)phenyl	388
2-(2-propyl)phenoxy	3-chlorophenyl	366
2-(2-propyl)phenoxy	2-nitrophenyl	377
2-(2-propyl)phenoxy	3, 5-dimethoxyphenyl	399
2-(2-propyl)phenoxy	2, 6-dichlorophenyl	400
2-(2-propyl)phenoxy	2, 4-dichlorophenyl	400

71	72	71	72
2-(2-propyl)phenoxy	3-pyridyl	3-fluoro-5-methylphenoxy	323
2-(2-propyl)phenoxy	pyridin-4-yl	2-ethoxynaphth-1-yl	416
anthraquinon-2-yl	333	3-fluoro-5-methylphenoxy	462
2-iodophenyl	462	3-fluoro-5-methylphenoxy	458
4-biphenyl	458	3-fluoro-5-methylphenoxy	398
3-fluoro-5-methylphenoxy	398	3-fluoro-5-methylphenoxy	382
3-fluoro-5-methylphenoxy	382	3,4-dimethoxyphenyl	382
3-fluoro-5-methylphenoxy	382	3-fluoro-5-methylphenoxy	358
2-(trifluoromethyl)phenyl	358	3-fluoro-5-methylphenoxy	390
3-fluoro-5-methylphenoxy	390	2,4-difluorophenyl	347
3-fluoro-5-methylphenoxy	347	4-cyanophenyl	358
3-fluoro-5-methylphenoxy	358	3-fluoro-5-methylphenoxy	390
3-(trifluoromethyl)phenyl	390	3-fluoro-5-methylphenoxy	347
3-fluoro-5-methylphenoxy	347	2-naphthyl	372
3-fluoro-5-methylphenoxy	372	2-methoxyphenyl	352
3-fluoro-5-methylphenoxy	352	3,4,5,-trimethylphenyl	412
3-fluoro-5-methylphenoxy	412	4-nitrophenyl	367
3-fluoro-5-methylphenoxy	367	3,4-dichlorophenyl	391
3-fluoro-5-methylphenoxy	391	5-nitrofuran-2-yl	357
3-fluoro-5-methylphenoxy	357	3-bromophenyl	401
3-fluoro-5-methylphenoxy	401	methoxyphenyl	
methoxyphenyl		3-chlorothien-2-yl	363
methoxyphenyl		3-fluoro-5-methylphenoxy	382
methoxyphenyl		1-(2-(2-methylpropyl)-3-methylpyrazol-5-yl	

73

74

3-fluoro-5-methylphenoxy	3,5-dichlorophenyl	391	3-fluoro-5-methylphenoxy	2-chloro-6-methylpyridin-4-yl	372
3-fluoro-5-methylphenoxy	2-(propylthio)pyridin-3-yl	397	3-fluoro-5-methylphenoxy	3,5-dimethylisoxazol-4-yl	341
3-fluoro-5-methylphenoxy	2-(ethylthio)pyridin-3-yl	383	3-fluoro-5-methylphenoxy	1-naphthyl	372
3-fluoro-5-methylphenoxy	3-bromopyridin-5-yl	402	3-fluoro-5-methylphenoxy	2-fluorophenyl	340
3-fluoro-5-methylphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	344	3-fluoro-5-methylphenoxy	4-propylphenyl	364
3-fluoro-5-methylphenoxy	1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl	382	3-fluoro-5-methylphenoxy	4-(trifluoromethyl)phenyl	390
3-fluoro-5-methylphenoxy	3-chlorobenzo[b]thiophen-2-yl	413	3-fluoro-5-methylphenoxy	3-fluorophenyl	340
3-fluoro-5-methylphenoxy	4-chlorophenyl	357	3-fluoro-5-methylphenoxy	2,6-difluorophenyl	358
3-fluoro-5-methylphenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	403	3-fluoro-5-methylphenoxy	2-chlorophenyl	357
3-fluoro-5-methylphenoxy	benzo[b]thiophen-2-yl	378	3-fluoro-5-methylphenoxy	3-(chloromethyl)phenyl	371
3-fluoro-5-methylphenoxy	3,4-dimethylphenyl	350	3-fluoro-5-methylphenoxy	4-(2-(2-methyl)propyl)phenyl	378
3-fluoro-5-methylphenoxy	2-(phenoxy)pyridin-3-yl	415	3-fluoro-5-methylphenoxy	3-chlorophenyl	357
3-fluoro-5-methylphenoxy	2-(methylthio)pyridin-3-yl	369	3-fluoro-5-methylphenoxy	2-nitrophenyl	367
3-fluoro-5-methylphenoxy	5-methyl-1,3-phenylisoxazol-4-yl	403	3-fluoro-5-methylphenoxy	3,5-dimethoxyphenyl	382
3-fluoro-5-methylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	426	3-fluoro-5-methylphenoxy	2,6-dichlorophenyl	391
			3-fluoro-5-methylphenoxy	2,6-difluorophenyl	

75

76

3-fluoro-5-methylphenoxy	2,4-dichlorophenyl	391	3-fluoro-5-methylphenoxy	thien-2-yl	328
3-fluoro-5-methylphenoxy	4-fluorophenyl	340	3-fluoro-5-methylphenoxy	2-bromophenyl	401
3-fluoro-5-methylphenoxy	4-butylophenyl	378	3-fluoro-5-methylphenoxy	4-bromophenyl	401
3-fluoro-5-methylphenoxy	2-methylphenyl	336	3-fluoro-5-methylphenoxy	4-fluoro-3-(trifluoromethoxy)phenyl	408
3-fluoro-5-methylphenoxy	phenyl	322	3-fluoro-5-methylphenoxy	3-(trifluoromethoxy)phenyl	406
3-fluoro-5-methylphenoxy	4-ethylphenyl	350	3-fluoro-5-methylphenoxy	9-fluoren-4-yl	424
3-fluoro-5-methylphenoxy	2,3-difluorophenyl	358	3-fluoro-5-methylphenoxy	isoxazol-5-yl	313
3-fluoro-5-methylphenoxy	2,6-dimethoxyphenyl	382	3-fluoro-5-methylphenoxy	benzofuroxan-5-yl	380
3-fluoro-5-methylphenoxy	3,4-difluorophenyl	358	3-fluoro-5-methylphenoxy	2-chloropyrid-3-yl	358
3-fluoro-5-methylphenoxy	2,5-difluorophenyl	358	3-fluoro-5-methylphenoxy	3,5-difluorophenyl	358
3-fluoro-5-methylphenoxy	4-ethoxyphenyl	366	3-fluoro-5-methylphenoxy	2-(4-methylphenoxy)pyridin-3-yl	429
3-fluoro-5-methylphenoxy	2,4,6-trichlorophenyl	426	3-fluoro-5-methylphenoxy	pyridin-4-yl	323
3-fluoro-5-methylphenoxy	3-methylphenyl	336	3-fluoro-5-methylphenoxy	anthraquinon-2-yl	452
3-fluoro-5-methylphenoxy	2-fluoro-5-(trifluoromethyl)phenyl	408	3-fluoro-5-methylphenoxy	2-iodophenyl	448
3-fluoro-5-methylphenoxy	3-methoxyphenyl	352	2-methylpyrid-3-yl	4-biphenyl	381
3-fluoro-5-methylphenoxy	2-methylpyrid-3-yl	365	2-methylpyrid-3-yl	3,4-dimethoxyphenyl	365

77

2-methylpyrid-3-yloxy 2-(trifluoromethyl)phenyl 373
 2-methylpyrid-3-yloxy 2,4-difluorophenyl 341
 2-methylpyrid-3-yloxy 4-cyanophenyl 330
 2-methylpyrid-3-yloxy 3-(trifluoromethyl)phenyl 373
 2-methylpyrid-3-yloxy 3-cyanophenyl 330
 2-methylpyrid-3-yloxy 2-naphthyl 355
 2-methylpyrid-3-yloxy 2-methoxyphenyl 335
 2-methylpyrid-3-yloxy 3,4,5-trimethylphenyl 395
 2-methylpyrid-3-yloxy 4-nitrophenyl 350
 2-methylpyrid-3-yloxy 3,4-dichlorophenyl 374
 2-methylpyrid-3-yloxy 5-nitrofuran-2-yl 340
 2-methylpyrid-3-yloxy 3-bromophenyl 384
 2-methylpyrid-3-yloxy 3-pyridyl 306
 2-methylpyrid-3-yloxy 2-ethoxynaphth-1-yl 399
 2-methylpyrid-3-yloxy 2,3-dichlorophenyl 374
 2-methylpyrid-3-yloxy 3-nitrophenyl 350
 2-methylpyrid-3-yloxy 6-chloropyrid-3-yl 341
 2-methylpyrid-3-yloxy 4-(trifluoromethoxy)phenyl 389
 2-methylpyrid-3-yloxy 2-fluoro-4-(trifluoromethyl)phenyl 391
 2-methylpyrid-3-yloxy 3-bromothiophenyl 390
 2-methylpyrid-3-yloxy 2-acetoxyphenyl 363
 2-methylpyrid-3-yloxy 5-methylisoxazol-3-yl 310
 2-methylpyrid-3-yloxy 2-(phenylthio)pyrid-3-yl 414
 2-methylpyrid-3-yloxy 2-(trifluoromethoxy)phenyl 389
 2-methylpyrid-3-yloxy 1-phenyl-5-propylpyrazin-4-yl 413
 2-methylpyrid-3-yloxy 2-ethoxyphenyl 349

78

2-methylpyrid-3-yloxy 3-chlorothien-2-yl 346
 2-methylpyrid-3-yloxy 1-(2-(2-methyl)propyl)pyridyl-3-yl 365
 2-methylpyrid-3-yloxy 3,5-dichlorophenyl 374
 2-methylpyrid-3-yloxy 2-(propylthio)pyridin-3-yl 380
 2-methylpyrid-3-yloxy 2-(ethylthio)pyridin-3-yl 366
 2-methylpyrid-3-yloxy 3-bromopyridin-5-yl 385
 2-methylpyrid-3-yloxy 4-methyl-1,2,3-thiadiazol-5-yl 327
 2-methylpyrid-3-yloxy 1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl 365
 2-methylpyrid-3-yloxy 3-chlorobenzo[b]thiophen-2-yl 396
 2-methylpyrid-3-yloxy 4-chlorophenyl 340
 2-methylpyrid-3-yloxy 4-methyl-1,2-phenyl-1,2,3-triazol-5-yl 386
 2-methylpyrid-3-yloxy 2,3-dimethylphenyl 361
 2-methylpyrid-3-yloxy 3,4-dimethylphenyl 333
 2-methylpyrid-3-yloxy 2-(phenoxy)pyridin-3-yl 398
 2-methylpyrid-3-yloxy 2-(methylthio)pyridin-3-yl 352
 2-methylpyrid-3-yloxy 5-methyl-3-phenylisoxazol-4-yl 386
 2-methylpyrid-3-yloxy 4-chloro-1,3-dimethylpyridin-3-yloxy 409
 2-methylpyrid-3-yloxy 2-chloro-6-methylpyridin-3-yloxy 355
 2-methylpyrid-3-yloxy 3,5-dimethylisoxazol-4-yl 324
 2-methylpyrid-3-yloxy 1-naphthyl 355
 2-methylpyrid-3-yloxy 2-fluorophenyl 323

2-methylpyrid-3-yloxy 4-propylphenyl	347	2-methylpyrid-3-yloxy thien-2-yl	311
2-methylpyrid-3-yloxy 4-(trifluoromethyl)phenyl	373	2-methylpyrid-3-yloxy 2-bromophenyl	384
2-methylpyrid-3-yloxy 3-fluorophenyl	323	2-methylpyrid-3-yloxy 4-bromophenyl	384
2-methylpyrid-3-yloxy 2-chlorophenyl	340	2-methylpyrid-3-yloxy 4-fluoro-3-(trifluoromethyl)phenyl	391
2-methylpyrid-3-yloxy 3-(chloromethyl)phenyl	354	2-methylpyrid-3-yloxy 3-(trifluoromethoxy)phenyl	389
2-methylpyrid-3-yloxy 4-(2-(2-methyl)propyl)phenyl	361	2-methylpyrid-3-yloxy 9-fluoren-4-yl	407
2-methylpyrid-3-yloxy 3-chlorophenyl	340	2-methylpyrid-3-yloxy isoxazol-5-yl	296
2-methylpyrid-3-yloxy 2-nitrophenyl	350	2-methylpyrid-3-yloxy benzofuran-5-yl	363
2-methylpyrid-3-yloxy 3,5-dimethoxyphenyl	365	2-methylpyrid-3-yloxy 2-chloropyrid-3-yl	341
2-methylpyrid-3-yloxy 2,6-dichlorophenyl	374	2-methylpyrid-3-yloxy 3,5-difluorophenyl	341
2-methylpyrid-3-yloxy 2,4-dichlorophenyl	374	2-methylpyrid-3-yloxy 2-(4-methylphenoxy)pyridin-3-yl	412
2-methylpyrid-3-yloxy 4-fluorophenyl	323	2-methylpyrid-3-yloxy pyridin-4-yl	306
2-methylpyrid-3-yloxy 4-butylphenyl	361	2-methylpyrid-3-yloxy anthraquinon-2-yl	435
2-methylpyrid-3-yloxy 2-methylphenyl	319	2-methylpyrid-3-yloxy 2-iodophenyl	431
2-methylpyrid-3-yloxy phenyl	305	4-chloro-2,5-dimethylphenoxy	413
2-methylpyrid-3-yloxy 4-ethylphenyl	333	4-chloro-2,5-dimethylphenoxy	413
2-methylpyrid-3-yloxy 2,3-difluorophenyl	341	4-chloro-2-(trifluoromethyl)phenyl	421
2-methylpyrid-3-yloxy 2,6-dimethoxyphenyl	365	4-chloro-2,5-dimethylphenoxy	413
2-methylpyrid-3-yloxy 3,4-difluorophenyl	341	4-chloro-2,5-dimethylphenoxy	413
2-methylpyrid-3-yloxy 2,5-difluorophenyl	341	4-chloro-2,5-dimethylphenoxy	413
2-methylpyrid-3-yloxy 4-ethoxyphenyl	349	4-chloro-2,5-dimethylphenoxy	413
2-methylpyrid-3-yloxy 2,4,6-trichlorophenyl	409	4-chloro-2,5-dimethylphenoxy	403
2-methylpyrid-3-yloxy 3-methylphenyl	319	4-chloro-2,5-dimethylphenoxy	403
2-methylpyrid-3-yloxy 2-fluoro-5-(trifluoromethyl)phenyl	391	4-chloro-2,5-dimethylphenoxy	403
2-methylpyrid-3-yloxy 3-methoxyphenyl	335	4-chloro-2,5-dimethylphenoxy	403

81

4-chloro-2,5-dimethylphenoxy	3,4-dichlorophenyl	422	4-chloro-2,5-dimethylphenoxy	1-(2-(2-methyl)propyl)pyridin-3-yl	413
4-chloro-2,5-dimethylphenoxy	3-bromophenyl	432	4-chloro-2,5-dimethylphenoxy	3,5-dichlorophenyl	422
4-chloro-2,5-dimethylphenoxy	3-pyridyl	354	4-chloro-2,5-dimethylphenoxy	2-(propylthio)pyridin-3-yl	428
4-chloro-2,5-dimethylphenoxy	2-ethoxynaphth-1-yl	447	4-chloro-2,5-dimethylphenoxy	2-(ethylthio)pyridin-3-yl	414
4-chloro-2,5-dimethylphenoxy	2,3-dichlorophenyl	422	4-chloro-2,5-dimethylphenoxy	3-bromopyridin-5-yl	433
4-chloro-2,5-dimethylphenoxy	6-chloropyrid-3-yl	388	4-chloro-2,5-dimethylphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	375
4-chloro-2,5-dimethylphenoxy	4-(trifluoromethoxy)phenyl	437	4-chloro-2,5-dimethylphenoxy	1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl	413
4-chloro-2,5-dimethylphenoxy	2-fluoro-4-(trifluoromethyl)phenyl	439	4-chloro-2,5-dimethylphenoxy	3-chlorobenzo[b]thiophen-2-yl	443
4-chloro-2,5-dimethylphenoxy	3-bromothienyl	438	4-chloro-2,5-dimethylphenoxy	4-chlorophenyl	387
4-chloro-2,5-dimethylphenoxy	2-acetoxyphenyl	411	4-chloro-2,5-dimethylphenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	434
4-chloro-2,5-dimethylphenoxy	5-methylisoxazol-3-yl	358	4-chloro-2,5-dimethylphenoxy	benzo[b]thiophen-2-yl	409
4-chloro-2,5-dimethylphenoxy	2-(phenylthio)pyrid-3-yl	462	4-chloro-2,5-dimethylphenoxy	3,4-dimethylphenyl	381
4-chloro-2,5-dimethylphenoxy	2-(trifluoromethoxy)phenyl	437	4-chloro-2,5-dimethylphenoxy	2-(phenoxy)pyridin-3-yl	446
4-chloro-2,5-dimethylphenoxy	1-phenyl-5-propylpyrazin-4-yl	461	4-chloro-2,5-dimethylphenoxy	2-(methylthio)pyridin-3-yl	400
4-chloro-2,5-dimethylphenoxy	2-ethoxyphenyl	397	5-methyl-3-phenylisoxazol-4-yl	5-methyl-3-phenylisoxazol-4-yl	434
4-chloro-2,5-dimethylphenoxy	3-chlorothien-2-yl	393	4-chloro-2,5-dimethylphenoxy	3-chlorothien-2-yl	393

83

84

4-chloro-2,5-dimethylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	4-chloro-2,5-dimethylphenoxy	4-chloro-2,5-dimethylphenoxy
2-chloro-6-methylpyridin-4-yl	2-chloro-6-methylpyridin-4-yl	2-chloro-6-methylpyridin-4-yl	2-methylphenyl	2-methylphenyl
3,5-dimethylisoxazol-4-yl	3,5-dimethylisoxazol-4-yl	3,5-dimethylisoxazol-4-yl	phenyl	phenyl
1-naphthyl	1-naphthyl	1-naphthyl	4-chloro-2,5-dimethylphenoxy	4-chloro-2,5-dimethylphenoxy
2-fluorophenyl	2-fluorophenyl	2-fluorophenyl	2,3-difluorophenyl	2,3-difluorophenyl
4-propylphenyl	4-propylphenyl	4-propylphenyl	2,6-dimethoxyphenyl	2,6-dimethoxyphenyl
3-fluorophenyl	3-fluorophenyl	3-fluorophenyl	3,4-difluorophenyl	3,4-difluorophenyl
2,6-difluorophenyl	2,6-difluorophenyl	2,6-difluorophenyl	2,5-difluorophenyl	2,5-difluorophenyl
2-chlorophenyl	2-chlorophenyl	2-chlorophenyl	4-ethoxyphenyl	4-ethoxyphenyl
3-(chloromethyl)phenyl	3-(chloromethyl)phenyl	3-(chloromethyl)phenyl	2,4,6-trichlorophenyl	2,4,6-trichlorophenyl
401	401	401	456	456
4-chloro-2,5-dimethylphenoxy	4-chloro-2,5-dimethylphenoxy	4-chloro-2,5-dimethylphenoxy	3-methylphenyl	3-methylphenyl
4-(2-(2-methyl)propyl)phenyl	4-(2-(2-methyl)propyl)phenyl	4-(2-(2-methyl)propyl)phenyl	(trifluoromethyl)phenyl	(trifluoromethyl)phenyl
3-chlorophenyl	3-chlorophenyl	3-chlorophenyl	3-methoxyphenyl	3-methoxyphenyl
3,5-dimethoxyphenyl	3,5-dimethoxyphenyl	3,5-dimethoxyphenyl	2-bromophenyl	2-bromophenyl
4-chloro-2,5-dimethylphenoxy	4-chloro-2,5-dimethylphenoxy	4-chloro-2,5-dimethylphenoxy	4-bromophenyl	4-bromophenyl
2,6-dichlorophenyl	2,6-dichlorophenyl	2,6-dichlorophenyl	432	432
2,4-dichlorophenyl	2,4-dichlorophenyl	2,4-dichlorophenyl	432	432
dimethylphenoxy	dimethylphenoxy	dimethylphenoxy	dimethylphenoxy	dimethylphenoxy

85

4-chloro-2,5-dimethylphenoxy	4-fluoro-3-(trifluoromethoxy)phenyl	439
4-chloro-2,5-dimethylphenoxy	3-(trifluoromethoxy)phenyl	437
4-chloro-2,5-dimethylphenoxy	9-fluoren-4-yl	455
4-chloro-2,5-dimethylphenoxy	isoxazol-5-yl	344
4-chloro-2,5-dimethylphenoxy	benzofuran-5-yl	411
4-chloro-2,5-dimethylphenoxy	2-chloropyrid-3-yl	388
4-chloro-2,5-dimethylphenoxy	2-(4-methoxyphenoxy)pyridin-3-yl	460
4-chloro-2,5-dimethylphenoxy	pyridin-4-yl	354
4-chloro-2,5-dimethylphenoxy	anthraquinon-2-yl	483
4-chloro-2,5-dimethylphenoxy	2-iodophenyl	479
4-chloro-2,5-dimethylphenoxy	4-pentylphenyl	423
4-chloro-2,5-dimethylphenoxy	2-(4-chlorophenylthio)pyridin-3-yl	496
4-chloro-2,5-dimethylphenoxy	2,6-dimethylphenyl	381
4-chloro-2,5-dimethylphenoxy	2,5-dimethoxyphenyl	413
4-chloro-2,5-dimethylphenoxy	2,5-dichloropyridin-3-yl	423
4-chloro-2,5-dimethylphenoxy	2-chloro-6-methoxypyridin-4-yl	418

86

4-chloro-2,5-dimethylphenoxy	4-chloro-2,5-dimethylphenoxy	423
4-chloro-2,5-dimethylphenoxy	1-naphthyl	417
4-chloro-2,5-dimethylphenoxy	2,4-dimethoxyphenyl	413
4-chloro-2,5-dimethylphenoxy	3,5-bis(trifluoromethyl)phenyl	489
4-chloro-2,5-dimethylphenoxy	2-(4-chlorophenoxy)pyridin-3-yl	480
4-chloro-2,5-dimethylphenoxy	pentafluorophenyl	443
4-methoxyphenoxy	3,4-dimethoxyphenyl	380
4-methoxyphenoxy	2-(trifluoromethyl)phenyl	388
4-methoxyphenoxy	2,4-difluorophenyl	356
4-methoxyphenoxy	3-(trifluoromethyl)phenyl	388
4-methoxyphenoxy	2-naphthyl	370
4-methoxyphenoxy	2-methoxyphenyl	350
4-methoxyphenoxy	3,4,5-trimethylphenyl	410
4-methoxyphenoxy	3,4-dichlorophenyl	389
4-methoxyphenoxy	3-bromophenyl	399
4-methoxyphenoxy	3-pyridyl	321
4-methoxyphenoxy	2-ethoxy[naphth-1-yl]	414
4-methoxyphenoxy	2,3-dichlorophenyl	389
4-methoxyphenoxy	6-chloropyrid-3-yl	356
4-methoxyphenoxy	4-(trifluoromethoxy)phenyl	404
4-methoxyphenoxy	2-fluoro-4-(trifluoromethyl)phenyl	406
4-methoxyphenoxy	3-bromothienyl	405

		87	88	
4-methoxyphenoxy	2-acetoxyphenyl	378	4-methoxyphenoxy	
4-methoxyphenoxy	5-methylisoxazol-3-yl	325	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	424
4-methoxyphenoxy	2-(phenylthio)pyrid-3-yl	429	2-chloro-6-methylpyridin-4-yl	370
4-methoxyphenoxy	2-(trifluoromethoxy)phenyl	404	3,5-dimethylisoxazol-4-yl	339
4-methoxyphenoxy	1-phenyl-5-propylpyrazin-4-yl	428	1-naphthyl	370
4-methoxyphenoxy	2-ethoxyphenyl	364	2-fluorophenyl	338
4-methoxyphenoxy	3-chlorothien-2-yl	361	4-propylphenyl	362
4-methoxyphenoxy	1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl	380	3-fluorophenyl	338
4-methoxyphenoxy	3,5-dichlorophenyl	389	2,6-difluorophenyl	356
4-methoxyphenoxy	2-(propylthio)pyridin-3-yl	395	2-chlorophenyl	355
4-methoxyphenoxy	2-(ethylthio)pyridin-3-yl	381	3-(chloromethyl)phenyl	369
4-methoxyphenoxy	3-bromopyridin-5-yl	400	4-(2-(2-methylpropyl)phenyl	376
4-methoxyphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	342	3-chlorophenyl	355
4-methoxyphenoxy	1-methyl-3-(2-(2-methylpropyl)pyrazol-5-yl	380	3,5-dimethoxyphenyl	380
4-methoxyphenoxy	3-chlorobenzo[b]thiophen-2-yl	411	2,6-dichlorophenyl	389
4-methoxyphenoxy	4-chlorophenyl	355	2,4-dichlorophenyl	389
4-methoxyphenoxy	4-methyl-1,2-phenyl-1,2,3-triazol-5-yl	401	4-fluorophenyl	338
4-methoxyphenoxy	benzo[b]thiophen-2-yl	376	4-butylphenyl	376
4-methoxyphenoxy	3,4-dimethylphenyl	348	2-methylphenyl	334
4-methoxyphenoxy	2-(phenoxy)pyridin-3-yl	413	phenyl	320
4-methoxyphenoxy	2-(methylthio)pyridin-3-yl	367	4-ethylphenyl	348
4-methoxyphenoxy	5-methyl-3-phenylisoxazol-4-yl	401	2,3-difluorophenyl	356
4-methoxyphenoxy	4-yl	364	4-methoxyphenyl	380
	4-methoxyphenyl		2,5-dimethoxyphenyl	380
			3,4-difluorophenyl	356
			2,5-difluorophenyl	356
			4-ethoxyphenyl	364

4-methoxyphenoxy	2,4,6-trichlorophenyl	424	90
4-methoxyphenoxy	3-methylphenyl	334	424
4-methoxyphenoxy	2-fluoro-5-(trifluoromethyl)phenyl	406	334
4-methoxyphenoxy	3-methoxyphenoxy	350	2-fluoro-5-(trifluoromethyl)phenyl
4-methoxyphenoxy	2-bromophenyl	399	406
4-methoxyphenoxy	4-bromophenyl	399	350
4-methoxyphenoxy	4-fluoro-3-(trifluoromethyl)phenyl	406	399
4-methoxyphenoxy	3-(trifluoromethoxy)phenyl	404	399
4-methoxyphenoxy	9-fluoren-4-yl	422	406
4-methoxyphenoxy	isoxazol-5-yl	311	422
4-methoxyphenoxy	benzofuroxan-5-yl	378	311
4-methoxyphenoxy	2-chloropyrid-3-yl	356	378
4-methoxyphenoxy	2-(4-methylphenoxy)pyridin-3-yl	427	356
4-methoxyphenoxy	pyridin-4-yl	321	427
4-methoxyphenoxy	anthraquinon-2-yl	450	321
4-methoxyphenoxy	2-iodophenyl	446	450
4-methoxyphenoxy	4-pentylphenyl	390	446
4-methoxyphenoxy	2-(4-chlorophenylthio)pyridin-3-yl	464	390
4-methoxyphenoxy	2,6-dimethylphenyl	348	464
4-methoxyphenoxy	2,5-dimethoxyphenyl	380	348
4-methoxyphenoxy	2,5-dichloropyridin-3-yl	390	380
4-methoxyphenoxy	2-chloro-6-methoxypyridin-4-yl	386	390
4-methoxyphenoxy	2,3-dichloropyridin-5-yl	390	386
4-methoxyphenoxy	1-naphthyl	384	390
4-methoxyphenoxy	2,4-dimethoxyphenyl	380	384
4-methoxyphenoxy	3,5-bis(trifluoromethyl)phenyl	456	380
4-methoxyphenoxy	2-(4-chlorophenoxy)pyridin-3-yl	448	456
4-methoxyphenoxy	pentafluorophenyl	410	448
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	408	410
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	416	408
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	384	416
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	384	384
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	416	384
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	398	416
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	378	398
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	438	378
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	417	438
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	427	417
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	349	427
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	442	349
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	417	442
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	384	417
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	432	384
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	434	432
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	433	434
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	406	433
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	353	406
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	458	353
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	432	458
4-methoxyphenoxy	2-(2-propoxy)phenoxyl	432	432

91

92

2-(2-propoxy)phenoxy	2-ethoxyphenyl	392	2-(2-propoxy)phenoxy	2-fluorophenyl	366
2-(2-propoxy)phenoxy	3-chlorothien-2-yl	389	2-(2-propoxy)phenoxy	4-propylphenyl	390
2-(2-propoxy)phenoxy	1-(2-(2-methylpropyl)propyl)-3-methylpyrazol-5-yl	408	2-(2-propoxy)phenoxy	3-fluorophenyl	366
2-(2-propoxy)phenoxy	3,5-dichlorophenyl	417	2-(2-propoxy)phenoxy	2,6-di fluorophenyl	384
2-(2-propoxy)phenoxy	2-(propylthio)pyridin-3-yl	423	2-(2-propoxy)phenoxy	2-chlorophenyl	383
2-(2-propoxy)phenoxy	2-(ethylthio)pyridin-3-yl	409	2-(2-propoxy)phenoxy	3-(chloromethyl)phenyl	397
2-(2-propoxy)phenoxy	3-bromopyridin-5-yl	428	2-(2-propoxy)phenoxy	4-(2-(2-methylpropyl)phenyl	404
2-(2-propoxy)phenoxy	4-methyl-1,1,2,3-thiadiazol-5-yl	370	2-(2-propoxy)phenoxy	3-chlorophenyl	383
2-(2-propoxy)phenoxy	1-methyl-1,3-(2-(2-methylpropyl)propyl)pyrazol-5-yl	408	2-(2-propoxy)phenoxy	3,5-dimethoxyphenyl	408
2-(2-propoxy)phenoxy	3-chlorobenzo[b]thiophen-2-yl	439	2-(2-propoxy)phenoxy	2,6-dichlorophenyl	417
2-(2-propoxy)phenoxy	4-chlorophenyl	383	2-(2-propoxy)phenoxy	2,4-dichlorophenyl	417
2-(2-propoxy)phenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	429	2-(2-propoxy)phenoxy	4-fluorophenyl	366
2-(2-propoxy)phenoxy	benzo[b]thiophen-2-yl	404	2-(2-propoxy)phenoxy	4-butylphenyl	404
2-(2-propoxy)phenoxy	3,4-dimethylphenyl	376	2-(2-propoxy)phenoxy	2-methylphenyl	362
2-(2-propoxy)phenoxy	2-(phenoxy)pyridin-3-yl	441	2-(2-propoxy)phenoxy	phenyl	348
2-(2-propoxy)phenoxy	5-methyl-3-phenylisoxazol-4-yl	429	2-(2-propoxy)phenoxy	4-ethylphenyl	376
2-(2-propoxy)phenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	452	2-(2-propoxy)phenoxy	2,3-difluorophenyl	384
2-(2-propoxy)phenoxy	4-yl	398	2-(2-propoxy)phenoxy	2,6-dimethoxyphenyl	408
2-(2-propoxy)phenoxy	3,5-dimethylisoxazol-4-yl	367	2-(2-propoxy)phenoxy	3,4-difluorophenyl	384
2-(2-propoxy)phenoxy	1-naphthyl	398	2-(2-propoxy)phenoxy	2,5-difluorophenyl	384

93

2-(2-propoxy)phenoxy	4-bromophenyl	427
2-(2-propoxy)phenoxy	4-Fluoro-3-(trifluoromethyl)phenyl	434
2-(2-propoxy)phenoxy	3-(trifluoromethoxy)phenyl	432
2-(2-propoxy)phenoxy	9-fluoren-4-yl	450
2-(2-propoxy)phenoxy	isoxazol-5-yl	339
2-(2-propoxy)phenoxy	benzfuroxan-5-yl	406
2-(2-propoxy)phenoxy	2-chloropyrid-3-yl	384
2-(2-propoxy)phenoxy	2-(4-methylphenoxy)pyridin-3-yl	455
2-(2-propoxy)phenoxy	pyridin-4-yl	349
2-(2-propoxy)phenoxy	anthraquinon-2-yl	478
2-(2-propoxy)phenoxy	2-iodophenyl	474
2-(2-propoxy)phenoxy	4-pentylophenyl	419
2-(2-propoxy)phenoxy	2-(4-chlorophenylthio)pyridin-3-yl	492
2-(2-propoxy)phenoxy	2,6-dimethylphenyl	376
2-(2-propoxy)phenoxy	2,5-dimethoxyphenyl	408
2-(2-propoxy)phenoxy	2,5-dichloropyridin-3-yl	418
2-(2-propoxy)phenoxy	2-chloro-6-methoxypyridin-4-yl	414
2-(2-propoxy)phenoxy	2,3-dichloropyridin-5-yl	418
2-(2-propoxy)phenoxy	1-naphthyl	412
2-(2-propoxy)phenoxy	2,4-dimethoxyphenyl	408
2-(2-propoxy)phenoxy	3,5-bis(trifluoromethyl)phenyl	484
2-(2-propoxy)phenoxy	2-(4-chlorophenoxy)pyridin-3-yl	476
2-(2-propoxy)phenoxy	pentafluorophenyl	438

94

4-fluorophenoxy	3,4-dimethoxyphenyl	368
4-fluorophenoxy	2-(trifluoromethyl)phenyl	376
4-fluorophenoxy	2,4-difluorophenyl	344
4-fluorophenoxy	3-(trifluoromethyl)phenyl	376
4-fluorophenoxy	4-naphthyl	358
4-fluorophenoxy	2-methoxyphenyl	338
4-fluorophenoxy	3,4,5-trimethylphenyl	398
4-fluorophenoxy	3,4-dichlorophenyl	377
4-fluorophenoxy	3-bromophenyl	387
4-fluorophenoxy	3-pyridyl	309
4-fluorophenoxy	2-ethoxynaphth-1-yl	402
4-fluorophenoxy	2,3-dichlorophenyl	377
4-fluorophenoxy	6-chloropyrid-3-yl	344
4-fluorophenoxy	4-(trifluoromethoxy)phenyl	392
4-fluorophenoxy	2-fluoro-4-(trifluoromethyl)phenyl	394
4-fluorophenoxy	3-bromothiophenyl	393
4-fluorophenoxy	2-acetoxyphenyl	366
4-fluorophenoxy	5-methylisoxazol-3-yl	313
4-fluorophenoxy	2-(phenylthio)pyrid-3-yl	417
4-fluorophenoxy	2-(trifluoromethoxy)phenyl	392
4-fluorophenoxy	1-phenyl-5-propylpyrazin-4-yl	416
4-fluorophenoxy	2-ethoxyphenyl	352
4-fluorophenoxy	3-chlorothien-2-yl	349
4-fluorophenoxy	1-(2-(2-methylpropyl)propyl)-3-methylpyrazol-5-yl	368
4-fluorophenoxy	3,5-dichlorophenyl	377

95

96

4-fluorophenoxy	2-(propylthio)pyridin-3-yl	383	4-fluorophenoxy	3-(chloromethyl)phenyl	357
4-fluorophenoxy	2-(ethylthio)pyridin-3-yl	369	4-fluorophenoxy	4-(2-(2-methylpropyl)phenyl	364
4-fluorophenoxy	3-bromopyridin-5-yl	388	4-fluorophenoxy	3-chlorophenyl	343
4-fluorophenoxy	4-methyl-1,2,3-thiadiazol-5-yl	330	4-fluorophenoxy	3,5-dimethoxyphenyl	368
4-fluorophenoxy	1-methyl-3-(2-(2-methylpropyl)pyrazol-5-yl)2-yl	368	4-fluorophenoxy	2,6-dichlorophenyl	377
4-fluorophenoxy	3-chlorobenzo[b]thiophen-2-yl	399	4-fluorophenoxy	2,4-dichlorophenyl	377
4-fluorophenoxy	4-chlorophenyl	343	4-fluorophenoxy	4-fluorophenyl	326
4-fluorophenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	389	4-fluorophenoxy	4-butylphenyl	364
4-fluorophenoxy	benzo[b]thiophen-2-yl	364	4-fluorophenoxy	2-methylphenyl	322
4-fluorophenoxy	3,4-dimethylphenyl	336	4-fluorophenoxy	4-ethylphenyl	308
4-fluorophenoxy	2-(phenoxy)pyridin-3-yl	401	4-fluorophenoxy	2,3-difluorophenyl	344
4-fluorophenoxy	2-(methylthio)pyridin-3-yl	355	4-fluorophenoxy	2,6-dimethoxyphenyl	368
4-fluorophenoxy	5-methyl-3-phenylisoxazol-4-yl	389	4-fluorophenoxy	3,4-difluorophenyl	344
4-fluorophenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	412	4-fluorophenoxy	2,5-difluorophenyl	344
4-fluorophenoxy	2-chloro-6-methylpyridin-4-yl	358	4-fluorophenoxy	4-ethoxyphenyl	352
4-fluorophenoxy	3,5-dimethylisoxazol-4-yl	327	4-fluorophenoxy	2,4,6-trichlorophenyl	412
4-fluorophenoxy	1-naphthyl	358	4-fluorophenoxy	3-methylphenyl	322
4-fluorophenoxy	2-fluorophenyl	326	4-fluorophenoxy	2-fluoro-5-(trifluoromethyl)phenyl	394
4-fluorophenoxy	4-propylphenyl	350	4-fluorophenoxy	3-methoxyphenyl	338
4-fluorophenoxy	3-fluorophenyl	326	4-fluorophenoxy	2-bromophenyl	387
4-fluorophenoxy	2,6-difluorophenyl	344	4-fluorophenoxy	4-bromophenyl	387
4-fluorophenoxy	2-chlorophenyl	343	4-fluorophenoxy	4-fluoro-3-(trifluoromethyl)phenyl	394

97

98

4-fluorophenoxy	isoxazol-5-yl	299	4-chlorophenoxy	2-methoxyphenyl	355
4-fluorophenoxy	benzofuran-5-yl	366	4-chlorophenoxy	3,4,5-trimethylphenyl	415
4-fluorophenoxy	2-chloropyrid-3-yl	344	4-chlorophenoxy	3,4-dichlorophenyl	394
4-fluorophenoxy	2-(4-methylphenoxy)pyridin-3-yl	415	4-chlorophenoxy	3-bromophenyl	404
4-fluorophenoxy	pyridin-4-yl	309	4-chlorophenoxy	3-pyridyl	326
4-fluorophenoxy	anthraquinon-2-yl	438	4-chlorophenoxy	2-ethoxyxanth-1-yl	419
4-fluorophenoxy	2-iodophenyl	434	4-chlorophenoxy	2,3-dichlorophenyl	394
4-fluorophenoxy	4-pentylphenyl	378	4-chlorophenoxy	6-chloropyrid-3-yl	360
4-fluorophenoxy	2-(4-chlorophenylthio)pyridin-3-yl	452	4-chlorophenoxy	4-(trifluoromethoxy)phenyl	409
4-fluorophenoxy	2,6-dimethylphenyl	336	4-chlorophenoxy	2-fluoro-4-(trifluoromethyl)phenyl	411
4-fluorophenoxy	2,5-dimethoxyphenyl	368	4-chlorophenoxy	3-bromothietyl	410
4-fluorophenoxy	2,5-dichloropyridin-3-yl	378	4-chlorophenoxy	2-acetoxymethyl	383
4-fluorophenoxy	2-chloro-6-methoxypyridin-4-yl	374	4-chlorophenoxy	5-methylisoxazol-3-yl	330
4-fluorophenoxy	2,3-dichloropyridin-5-yl	378	4-chlorophenoxy	2-(phenylthio)pyrid-3-yl	434
4-fluorophenoxy	1-naphthyl	372	4-chlorophenoxy	2-(trifluoromethoxy)phenyl	409
4-fluorophenoxy	2,4-dimethoxyphenyl	368	4-chlorophenoxy	1-phenyl-5-propylpyrazin-4-yl	433
4-fluorophenoxy	3,5-bis(trifluoromethyl)phenyl	444	4-chlorophenoxy	2-ethoxyphenyl	369
4-fluorophenoxy	2-(4-chlorophenoxy)pyridin-3-yl	436	4-chlorophenoxy	3-chlorothien-2-yl	365
4-fluorophenoxy	5-pentafluorophenyl	398	4-chlorophenoxy	1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl	385
4-fluorophenoxy	3,4-dimethoxyphenyl	385	4-chlorophenoxy	3,5-dichlorophenyl	394
4-fluorophenoxy	2-(trifluoromethyl)phenyl	393	4-chlorophenoxy	2-(propylthio)pyridin-3-yl	400
4-fluorophenoxy	2,4-difluorophenyl	361	4-chlorophenoxy	2-(ethylthio)pyridin-3-yl	386
4-fluorophenoxy	3-(trifluoromethyl)phenyl	393	4-chlorophenoxy	3-bromopyridin-5-yl	405
4-fluorophenoxy	2-naphthyl	375	4-chlorophenoxy	4-methyl-1,2,3-thiadiazol-5-yl	347

99

100

4-chlorophenoxy	1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl	385	4-chlorophenoxy	3,5-dimethoxyphenyl	385
4-chlorophenoxy	3-chlorobenzol[b]thiophen-2-yl	415	4-chlorophenoxy	2,6-dichlorophenyl	394
4-chlorophenoxy	4-chlorophenyl	359	4-chlorophenoxy	2,4-dichlorophenyl	394
4-chlorophenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	406	4-chlorophenoxy	4-fluorophenyl	343
4-chlorophenoxy	benzo[b]thiophen-2-yl	381	4-chlorophenoxy	4-butylophenyl	381
4-chlorophenoxy	3,4-dimethylphenyl	353	4-chlorophenoxy	2-methylphenyl	339
4-chlorophenoxy	2-(phenoxy)pyridin-3-yl	418	4-chlorophenoxy	4-ethylphenyl	325
4-chlorophenoxy	2-(methylthio)pyridin-3-yl	372	4-chlorophenoxy	4-ethoxyphenyl	353
4-chlorophenoxy	5-methyl-3-phenylisoxazol-4-yl	406	4-chlorophenoxy	2,3-difluorophenyl	361
4-chlorophenoxy	4-chlorophenoxy	428	4-chlorophenoxy	2,6-dimethoxyphenyl	385
4-chlorophenoxy	4-chlorophenoxy	374	4-chlorophenoxy	3,4-difluorophenyl	361
4-chlorophenoxy	2-chloro-6-methylpyridin-4-yl	344	4-chlorophenoxy	2,5-difluorophenyl	361
4-chlorophenoxy	1-naphthyl	375	4-chlorophenoxy	4-ethoxyphenyl	369
4-chlorophenoxy	2-fluorophenyl	343	4-chlorophenoxy	2,4,6-trichlorophenyl	428
4-chlorophenoxy	4-propylphenyl	367	4-chlorophenoxy	2-fluoro-5-(trifluoromethyl)phenyl	411
4-chlorophenoxy	3-fluorophenyl	343	4-chlorophenoxy	3-methoxyphenyl	339
4-chlorophenoxy	2,6-difluorophenyl	361	4-chlorophenoxy	2-bromophenyl	404
4-chlorophenoxy	2-chlorophenyl	359	4-chlorophenoxy	4-bromophenyl	404
4-chlorophenoxy	4-propylphenyl	367	4-chlorophenoxy	4-fluoro-3-(trifluoromethyl)phenyl	411
4-chlorophenoxy	3-fluorophenyl	343	4-chlorophenoxy	3-(trifluoromethoxy)phenyl	409
4-chlorophenoxy	2,6-difluorophenyl	361	4-chlorophenoxy	9-fluoren-4-yl	427
4-chlorophenoxy	2-chlorophenyl	359	4-chlorophenoxy	isoxazol-5-yl	316
4-chlorophenoxy	3-(chloromethyl)phenyl	373	4-chlorophenoxy	benzofuran-5-yl	383
4-chlorophenoxy	4-(2-(2-methyl)propyl)phenyl	381	4-chlorophenoxy	2-chloropyrid-3-yl	360
4-chlorophenoxy	3-chlorophenyl	359			

101

102

4-chlorophenoxy	2-(4-methylphenoxy)pyridin-3-yl	432	2,4-difluorophenoxy	3,4-dichlorophenyl	395
4-chlorophenoxy	pyridin-4-yl	326	2,4-difluorophenoxy	3-bromophenyl	405
4-chlorophenoxy	anthraquinon-2-yl	455	2,4-difluorophenoxy	3-pyridyl	327
4-chlorophenoxy	2-iodophenyl	451	2,4-difluorophenoxy	2-ethoxynaphth-1-yl	420
4-chlorophenoxy	4-pentylophenyl	395	2,4-difluorophenoxy	2,3-dichlorophenyl	395
4-chlorophenoxy	2-(4-chlorophenylthio)pyridin-3-yl	468	2,4-difluorophenoxy	6-chloropyrid-3-yl	362
4-chlorophenoxy	2,6-dimethylphenyl	353	2,4-difluorophenoxy	4-(trifluoromethoxy)phenyl	410
4-chlorophenoxy	2,5-dimethoxyphenyl	385	2,4-difluorophenoxy	2-fluoro-4-(trifluoromethyl)phenyl	412
4-chlorophenoxy	2,5-dichloropyridin-3-yl	395	2,4-difluorophenoxy	3-bromothienyl	411
4-chlorophenoxy	2-chloro-6-methoxypyridin-4-yl	390	2,4-difluorophenoxy	2-acetoxyphenyl	384
4-chlorophenoxy	2,3-dichloropyridin-5-yl	395	2,4-difluorophenoxy	5-methylisoxazol-3-yl	331
4-chlorophenoxy	1-naphthyl	389	2,4-difluorophenoxy	2-(phenylthio)pyrid-3-yl	435
4-chlorophenoxy	2,4-dimethoxyphenyl	385	2,4-difluorophenoxy	2-(trifluoromethoxy)phenyl	410
4-chlorophenoxy	3,5-bis(trifluoromethyl)phenyl	461	2,4-difluorophenoxy	1-phenyl-5-propylpyrazin-4-yl	434
4-chlorophenoxy	2-(4-chlorophenoxy)pyridin-3-yl	452	2,4-difluorophenoxy	2-ethoxyphenyl	370
4-chlorophenoxy	pentafluorophenyl	415	2,4-difluorophenoxy	3-chlorothien-2-yl	367
4-chlorophenoxy	3,4-dimethoxyphenyl	386	2,4-difluorophenoxy	1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl	386
4-chlorophenoxy	2-(trifluoromethyl)phenyl	394	2,4-difluorophenoxy	2,4-difluorophenyl	395
4-chlorophenoxy	2,4-difluorophenoxy	362	2,4-difluorophenoxy	2-(propylthio)pyridin-3-yl	401
4-chlorophenoxy	3-(trifluoromethyl)phenyl	394	2,4-difluorophenoxy	2-(ethylthio)pyridin-3-yl	387
4-chlorophenoxy	2-naphthyl	376	2,4-difluorophenoxy	3-bromopyridin-5-yl	406
4-chlorophenoxy	2-methoxyphenyl	356	2,4-difluorophenoxy	4-methyl-1,2,3-thiadiazol-5-yl	348
4-chlorophenoxy	3,4,5-trimethylphenyl	416	2,4-difluorophenoxy	1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl	386

103

104

2,4-difluorophenoxy	3-chlorobenzo[b]thiophen-2-yl	417	2,4-difluorophenoxy	2,4-dichlorophenyl	392
2,4-difluorophenoxy	4-chlorophenyl	361	2,4-difluorophenoxy	4-fluorophenyl	344
2,4-difluorophenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	407	2,4-difluorophenoxy	4-butylophenyl	382
2,4-difluorophenoxy	benzo[b]thiophen-2-yl	382	2,4-difluorophenoxy	2-methylphenyl	340
2,4-difluorophenoxy	3,4-dimethylphenyl	354	2,4-difluorophenoxy	phenyl	326
2,4-difluorophenoxy	2-(phenoxy)pyridin-3-yl	409	2,4-difluorophenoxy	4-ethylphenyl	354
2,4-difluorophenoxy	2-(methylthio)pyridin-3-yl	373	2,4-difluorophenoxy	2,3-difluorophenyl	362
2,4-difluorophenoxy	5-methyl-3-phenylisoxazol-4-yl	407	2,4-difluorophenoxy	2,6-dimethoxyphenyl	386
2,4-difluorophenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	430	2,4-difluorophenoxy	3,4-difluorophenyl	362
2,4-difluorophenoxy	2-chloro-6-methylpyridin-4-yl	376	2,4-difluorophenoxy	2,5-difluorophenyl	362
2,4-difluorophenoxy	3,5-dimethylisoxazol-4-yl	345	2,4-difluorophenoxy	4-ethoxyphenyl	370
2,4-difluorophenoxy	1-naphthyl	376	2,4-difluorophenoxy	2,4,6-trichlorophenyl	430
2,4-difluorophenoxy	2-fluorophenyl	344	2,4-difluorophenoxy	3-methylphenyl	340
2,4-difluorophenoxy	4-propylphenyl	368	2,4-difluorophenoxy	2-fluoro-5-(trifluoromethyl)phenyl	412
2,4-difluorophenoxy	3-fluorophenyl	344	2,4-difluorophenoxy	3-methoxyphenyl	356
2,4-difluorophenoxy	2,6-difluorophenyl	362	2,4-difluorophenoxy	2-bromophenyl	405
2,4-difluorophenoxy	2-chlorophenyl	361	2,4-difluorophenoxy	4-bromophenyl	405
2,4-difluorophenoxy	3-(chloromethyl)phenyl	375	2,4-difluorophenoxy	4-fluoro-3-(trifluoromethyl)phenyl	412
2,4-difluorophenoxy	4-(2-(2-methyl)propyl)phenyl	382	2,4-difluorophenoxy	3-(trifluoromethoxy)phenyl	410
2,4-difluorophenoxy	3-chlorophenyl	361	2,4-difluorophenoxy	9-fluoren-4-yl	428
2,4-difluorophenoxy	3-(chloromethyl)phenyl	375	2,4-difluorophenoxy	isoxazol-5-yl	317
2,4-difluorophenoxy	4-(2-(2-methyl)propyl)phenyl	382	2,4-difluorophenoxy	benzofuran-5-yl	384
2,4-difluorophenoxy	2,6-dimethoxyphenyl	395	2,4-difluorophenoxy	2-chloropyrid-3-yl	362
2,4-difluorophenoxy	3,5-dimethoxyphenyl	386	2,4-difluorophenoxy	2-(4-methylphenoxy)pyridin-3-yl	413
2,4-difluorophenoxy	2,6-dichlorophenyl	395	2,4-difluorophenoxy	pyridin-4-yl	327

105

2,4-difluorophenoxy anthraquinon-2-yl 456
 2,4-difluorophenoxy 2-iodophenyl 452
 2,4-difluorophenoxy 4-pentylphenyl 396
 2,4-difluorophenoxy 2-(4-chlorophenylthio) pyridin-3-yl 470

2,4-difluorophenoxy 2,6-dimethylphenyl 354
 2,4-difluorophenoxy 2,5-dimethoxyphenyl 386
 2,4-difluorophenoxy 2,5-dichloropyridin-3-yl 396
 2,4-difluorophenoxy 2-chloro-6-methoxypyridin-4-yl 392
 2,4-difluorophenoxy 2,3-dichloropyridin-5-yl 396
 2,4-difluorophenoxy 1-naphthyl 390
 2,4-difluorophenoxy 2,4-dimethoxyphenyl 386
 2,4-difluorophenoxy 3,5-bis(trifluoromethyl)phenyl 462
 2,4-difluorophenoxy 2-(4-chlorophenoxy)pyridin-3-yl 454
 2,4-difluorophenoxy pentafluorophenyl 416
 4-thiomethylphenoxy 3,4-dimethoxyphenyl 396
 4-thiomethylphenoxy 2-(trifluoromethyl)phenyl 404
 4-thiomethylphenoxy 2,4-difluorophenyl 372
 4-thiomethylphenoxy 3-(trifluoromethyl)phenyl 404
 4-thiomethylphenoxy 2-naphthyl 386
 4-thiomethylphenoxy 2-methoxyphenyl 366
 4-thiomethylphenoxy 3,4,5-trimethylphenyl 426
 4-thiomethylphenoxy 3,4-dichlorophenyl 405
 4-thiomethylphenoxy 3-bromophenyl 415
 4-thiomethylphenoxy 3-pyridyl 337
 4-thiomethylphenoxy 2-ethoxynaphth-1-yl 430

106

4-thiomethylphenoxy 2,3-dichlorophenyl 405
 4-thiomethylphenoxy 6-chloropyrid-3-yl 372
 4-thiomethylphenoxy 4-(trifluoromethoxy)phenyl 420
 4-thiomethylphenoxy 2-fluoro-4-(trifluoromethyl)phenyl 422

4-thiomethylphenoxy 3-bromothiényl 421
 4-thiomethylphenoxy 2-acetoxyphenyl 394

4-thiomethylphenoxy 5-methylisoxazol-3-yl 341
 4-thiomethylphenoxy 2-(phenylthio)pyrid-3-yl 446

4-thiomethylphenoxy 2-(trifluoromethoxy)phenyl 420
 4-thiomethylphenoxy 1-phenyl-3-propylpyrazin-4-yl 445

4-thiomethylphenoxy 2-ethoxyphenyl 380
 4-thiomethylphenoxy 3-chlorothien-2-yl 377

4-thiomethylphenoxy 1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl 396

4-thiomethylphenoxy 3,5-dichlorophenyl 405

4-thiomethylphenoxy 2-(propylthio)pyridin-3-yl 412

4-thiomethylphenoxy 4-(ethylthio)pyridin-3-yl 397

4-thiomethylphenoxy 3-bromopyridin-5-yl 416

4-thiomethylphenoxy 4-methyl-1,2,3-thiadiazol-5-yl 358

4-thiomethylphenoxy 1-methyl-1-(2-(2-methylpropyl)pyrazol-5-yl 396

3-chlorobenzo[b]thiophen-2-yl 427

4-chlorophenyl 371

4-thiomethylphenoxy 4-methyl-1,2-phenyl 417

107

108

4-thiomethylphenoxy	benzo[b]thiophen-2-yl	392	4-thiomethylphenoxy	4-ethylphenyl	364
4-thiomethylphenoxy	3,4-dimethylphenyl	364	4-thiomethylphenoxy	2,3-difluorophenyl	372
4-thiomethylphenoxy	2-(phenoxy)pyridin-3-yl	429	4-thiomethylphenoxy	2,6-dimethoxyphenyl	396
4-thiomethylphenoxy	2-(methylthio)pyridin-3-yl	383	4-thiomethylphenoxy	3,4-difluorophenyl	372
4-thiomethylphenoxy	5-methyl-3-phenylisoxazol-4-yl	417	4-thiomethylphenoxy	2,5-difluorophenyl	372
4-thiomethylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	440	4-thiomethylphenoxy	4-ethoxyphenyl	380
4-thiomethylphenoxy	2-chloro-6-methylpyridin-4-yl	386	4-thiomethylphenoxy	2,4,6-trichlorophenyl	440
4-thiomethylphenoxy	3,5-dimethylisoxazol-4-yl	355	4-thiomethylphenoxy	3-methylphenyl	350
4-thiomethylphenoxy	1-naphthyl	386	4-thiomethylphenoxy	2-fluoro-5-(trifluoromethyl)phenyl	422
4-thiomethylphenoxy	2-fluorophenyl	354	4-thiomethylphenoxy	3-methoxyphenyl	366
4-thiomethylphenoxy	4-propylphenyl	378	4-thiomethylphenoxy	2-bromophenyl	415
4-thiomethylphenoxy	3-fluorophenyl	354	4-thiomethylphenoxy	4-bromophenyl	415
4-thiomethylphenoxy	2,6-di fluorophenyl	372	4-thiomethylphenoxy	4-fluoro-3-(trifluoromethyl)phenyl	422
4-thiomethylphenoxy	2-chlorophenyl	371	4-thiomethylphenoxy	3-(trifluoromethoxy)phenyl	420
4-thiomethylphenoxy	3-(chloromethyl)phenyl	385	4-thiomethylphenoxy	9-fluorenon-4-yl	438
4-thiomethylphenoxy	4-(2-(2-methyl)propyl)phenyl	392	4-thiomethylphenoxy	isoxazol-5-yl	327
4-thiomethylphenoxy	3-chlorophenyl	371	4-thiomethylphenoxy	benzofuran-5-yl	394
4-thiomethylphenoxy	3,5-dimethoxyphenyl	396	4-thiomethylphenoxy	2-chloropyrid-3-yl	372
4-thiomethylphenoxy	2,6-dichlorophenyl	405	4-thiomethylphenoxy	2-(4-methylphenoxy)pyridin-3-yl	443
4-thiomethylphenoxy	2,4-dichlorophenyl	405	4-thiomethylphenoxy	pyridin-4-yl	337
4-thiomethylphenoxy	4-fluorophenyl	354	4-thiomethylphenoxy	anthraquinon-2-yl	466
4-thiomethylphenoxy	4-butylphenyl	392	4-thiomethylphenoxy	2-iodophenyl	462
4-thiomethylphenoxy	2-methylphenyl	350	4-thiomethylphenoxy	4-pentylophenyl	407
4-thiomethylphenoxy	phenyl	336	4-thiomethylphenoxy	2-(4-chlorophenylthio)pyridin-3-yl	480

109

4-thiomethylphenoxy 2,5-dimethoxyphenyl 396

4-thiomethylphenoxy 2,5-dichloropyridin-3-yl 406

4-thiomethylphenoxy 2-chloro-6-methoxypyridin-4-yl 402

4-thiomethylphenoxy 2,3-dichloropyridin-5-yl 406

4-thiomethylphenoxy 1-naphthyl 400

4-thiomethylphenoxy 2,4-dimethoxyphenyl 396

4-thiomethylphenoxy 3,5-bis(trifluoromethyl)phenyl 372

4-thiomethylphenoxy 2-(4-chlorophenoxy)pyridin-3-yl 464

4-thiomethylphenoxy pentfluorophenyl 426

4-(2-(2-methyl)propyl)phenoxy 3,4-dimethoxyphenyl 406

4-(2-(2-methyl)propyl)phenoxy 2-(trifluoromethyl)phenyl 414

4-(2-(2-methyl)propyl)phenoxy 2,4-difluorophenyl 382

4-(2-(2-methyl)propyl)phenoxy 3-(trifluoromethyl)phenyl 414

4-(2-(2-methyl)propyl)phenoxy 2-naphthyl 396

4-(2-(2-methyl)propyl)phenoxy 2-methoxyphenyl 376

4-(2-(2-methyl)propyl)phenoxy 3,4,5-trimethylphenyl 436

4-(2-(2-methyl)propyl)phenoxy 3,4-dichlorophenyl 415

4-(2-(2-methyl)propyl)phenoxy 3-bromophenyl 425

4-(2-(2-methyl)propyl)phenoxy 3-bromophenyl 406

110

4-(2-(2-methyl)propyl)phenoxy 3-pyridyl 347

4-(2-(2-methyl)propyl)phenoxy 2-ethoxynaphth-1-yl 441

4-(2-(2-methyl)propyl)phenoxy 2,3-dichlorophenyl 415

4-(2-(2-methyl)propyl)phenoxy 6-chloropyrid-3-yl 382

4-(2-(2-methyl)propyl)phenoxy 4-(trifluoromethoxy)phenyl 430

4-(2-(2-methyl)propyl)phenoxy 4-(2-(2-methyl)propyl)phenoxy 464

4-(2-(2-methyl)propyl)phenoxy (trifluoromethyl)phenyl 432

4-(2-(2-methyl)propyl)phenoxy 3-bromothiianyl 431

4-(2-(2-methyl)propyl)phenoxy 2-acetoxypyhenyl 404

4-(2-(2-methyl)propyl)phenoxy 5-methylisoxazol-3-yl 351

4-(2-(2-methyl)propyl)phenoxy 2-(phenylthio)pyrid-3-yl 456

4-(2-(2-methyl)propyl)phenoxy 2-(trifluoromethoxy)phenyl 430

4-(2-(2-methyl)propyl)phenoxy 1-phenyl-5-propylpyrazin-4-yl 455

4-(2-(2-methyl)propyl)phenoxy 2-ethoxypyhenyl 390

4-(2-(2-methyl)propyl)phenoxy 3-chlorothien-2-yl 387

4-(2-(2-methyl)propyl)phenoxy 1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl 406

111

112

4-(2-(2-methyl)propyl)phenoxy	3,5-dichlorophenyl	415	4-(2-(2-methyl)propyl)phenoxy	2-chloro-6-methylpyridin-4-yl	396
4-(2-(2-methyl)propyl)phenoxy	2-(propylthio)pyridin-3-yl	422	4-(2-(2-methyl)propyl)phenoxy	3,5-dimethylisoxazol-4-yl	365
4-(2-(2-methyl)propyl)phenoxy	2-(ethylthio)pyridin-3-yl	407	4-(2-(2-methyl)propyl)phenoxy	1-naphthyl	396
4-(2-(2-methyl)propyl)phenoxy	3-bromopyridin-5-yl	426	4-(2-(2-methyl)propyl)phenoxy	2-fluorophenyl	364
4-(2-(2-methyl)propyl)phenoxy	4-methyl-1,2,3-thiadiazol-5-yl	368	4-(2-(2-methyl)propyl)phenoxy	4-propylphenyl	388
4-(2-(2-methyl)propyl)phenoxy	1-methyl-3-(2-(2-methyl)propyl)phenoxy	406	4-(2-(2-methyl)propyl)phenoxy	3-fluorophenyl	364
4-(2-(2-methyl)propyl)phenoxy	1-methyl-3-(2-(2-methyl)propyl)phenoxy	437	4-(2-(2-methyl)propyl)phenoxy	2,6-difluorophenyl	382
4-(2-(2-methyl)propyl)phenoxy	2-yl	381	4-(2-(2-methyl)propyl)phenoxy	2-chlorophenyl	381
4-(2-(2-methyl)propyl)phenoxy	4-chlorophenyl	381	4-(2-(2-methyl)propyl)phenoxy	3-(chloromethyl)phenyl	395
4-(2-(2-methyl)propyl)phenoxy	4-methyl-2-phenyl-1,2,3-	427	4-(2-(2-methyl)propyl)phenoxy	4-(2-(2-methyl)propyl)phenoxy	402
4-(2-(2-methyl)propyl)phenoxy	benzo[b]thiophen-2-yl	402	4-(2-(2-methyl)propyl)phenoxy	4-(2-(2-methyl)propyl)phenoxy	381
4-(2-(2-methyl)propyl)phenoxy	3,4-dimethylphenyl	374	4-(2-(2-methyl)propyl)phenoxy	3,5-dimethoxyphenyl	406
4-(2-(2-methyl)propyl)phenoxy	2-(phenoxy)pyridin-3-yl	439	4-(2-(2-methyl)propyl)phenoxy	2,6-dichlorophenyl	415
4-(2-(2-methyl)propyl)phenoxy	5-methyl-3-phenylisoxazol-4-yl	427	4-(2-(2-methyl)propyl)phenoxy	2,4-dichlorophenyl	415
4-(2-(2-methyl)propyl)phenoxy	4-chloro-1,3-dimethyl-4-(2-(2-methyl)propyl)phenoxy	450	4-(2-(2-methyl)propyl)phenoxy	4-fluorophenyl	364
4-(2-(2-methyl)propyl)phenoxy	4-(2-(2-methyl)propyl)phenoxy	411	4-(2-(2-methyl)propyl)phenoxy	4-butylophenyl	402

113	4 - (2 - (2 - methyl) propyl) phenoxy	2-methylphenyl	360	4 - (2 - (2 - methyl) propyl) phenoxy	9 - fluoren-4-yl	448			
346	4 - (2 - (2 - methyl) propyl) phenoxy	phenyl	346	4 - (2 - (2 - methyl) propyl) phenoxy	isoxazol-5-yl	338			
374	4 - (2 - (2 - methyl) propyl) phenoxy	4-ethylphenyl	374	4 - (2 - (2 - methyl) propyl) phenoxy	benzofuran-5-yl	404			
382	4 - (2 - (2 - methyl) propyl) phenoxy	2,3-difluorophenyl	382	4 - (2 - (2 - methyl) propyl) phenoxy	2-chloropyrid-3-yl	382			
406	4 - (2 - (2 - methyl) propyl) phenoxy	2,6-dimethoxyphenyl	406	4 - (2 - (2 - methyl) propyl) phenoxy	2-(4 - (2 - (2 - methyl) propyl) phenoxy) pyridin-3-yl	454			
382	4 - (2 - (2 - methyl) propyl) phenoxy	3,4-difluorophenyl	382	4 - (2 - (2 - methyl) propyl) phenoxy	pyridin-4-yl	347			
382	4 - (2 - (2 - methyl) propyl) phenoxy	2,5-difluorophenyl	382	4 - (2 - (2 - methyl) propyl) phenoxy	2-(4 - (2 - (2 - methyl) propyl) phenoxy) anthraquinon-2-yl	476			
390	4 - (2 - (2 - methyl) propyl) phenoxy	4-ethoxyphenyl	390	4 - (2 - (2 - methyl) propyl) phenoxy	2-iodophenyl	472			
450	4 - (2 - (2 - methyl) propyl) phenoxy	2,4,6-trichlorophenyl	450	4 - (2 - (2 - methyl) propyl) phenoxy	4-pentylophenyl	417			
360	4 - (2 - (2 - methyl) propyl) phenoxy	3-methylphenyl	360	4 - (2 - (2 - methyl) propyl) phenoxy	2-(4-chlorophenylthio) pyridin-3-yl	490			
432	4 - (2 - (2 - methyl) propyl) phenoxy	2-fluoro-5 - trifluoromethylphenyl	432	4 - (2 - (2 - methyl) propyl) phenoxy	2,6-dimethylphenyl	374			
376	4 - (2 - (2 - methyl) propyl) phenoxy	3-methoxyphenyl	376	4 - (2 - (2 - methyl) propyl) phenoxy	2,5-dimethoxyphenyl	406			
425	4 - (2 - (2 - methyl) propyl) phenoxy	2-bromophenyl	425	4 - (2 - (2 - methyl) propyl) phenoxy	2,5-dichloropyridin-3-yl	416			
432	4 - (2 - (2 - methyl) propyl) phenoxy	4-bromophenyl	432	4 - (2 - (2 - methyl) propyl) phenoxy	2-chloro-6-methoxypyridin-5-yl	412			
430	4 - (2 - (2 - methyl) propyl) phenoxy	3-(trifluoromethoxy)phenyl	430	4 - (2 - (2 - methyl) propyl) phenoxy	2,3-dichloropyridin-4-yl	416			
					1-naphthyl	410			

115

116

4-(2-(2-methylpropyl)phenoxy	2,4-dimethoxyphenyl	406	2,3-dimethylphenoxy	1-phenyl-5-propylpyrazin-4-yl	426
4-(2-(2-methylpropyl)phenoxy	3,5-bis(trifluoromethyl)phenyl	482	2,3-dimethylphenoxy	2-ethoxyphenyl	362
4-(2-(2-methylpropyl)phenoxy	2-(4-pyridin-3-yl)chlorophenoxy	474	2,3-dimethylphenoxy	3-chlorotriien-2-yl	359
4-(2-(2-methylpropyl)phenoxy	pentafluorophenyl	436	2,3-dimethylphenoxy	1-(2-(2-methylpropyl)-3-methylpyrazol-5-yl	378
2,3-dimethylphenoxy	3,4-dimethoxyphenyl	378	2,3-dimethylphenoxy	3,5-dichlorophenyl	387
2,3-dimethylphenoxy	2-(trifluoromethyl)phenyl	386	2,3-dimethylphenoxy	2-(propylthio)pyridin-3-yl	393
2,3-dimethylphenoxy	2,4-difluorophenyl	354	2,3-dimethylphenoxy	2-(ethylthio)pyridin-3-yl	379
2,3-dimethylphenoxy	3-(trifluoromethyl)phenyl	386	2,3-dimethylphenoxy	3-bromopyridin-5-yl	398
2,3-dimethylphenoxy	2-naphthyl	368	2,3-dimethylphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	340
2,3-dimethylphenoxy	2-methoxyphenyl	348	2,3-dimethylphenoxy	1-methyl-3-(2-(2-methylpropyl)pyrazol-5-yl	378
2,3-dimethylphenoxy	3,4,5-trimethylphenyl	408	2,3-dimethylphenoxy	3-chlorobenz[b]thiophen-2-yl	409
2,3-dimethylphenoxy	3-bromophenyl	387	2,3-dimethylphenoxy	4-chlorophenyl	353
2,3-dimethylphenoxy	3-pyridyl	319	2,3-dimethylphenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	399
2,3-dimethylphenoxy	2-ethoxynaphth-1-yl	412	2,3-dimethylphenoxy	benzo[b]thiophen-2-yl	374
2,3-dimethylphenoxy	2,3-dichlorophenyl	387	2,3-dimethylphenoxy	3,4-dimethylphenyl	346
2,3-dimethylphenoxy	6-chloropyrid-3-yl	354	2,3-dimethylphenoxy	2,3-dimethylphenyl	411
2,3-dimethylphenoxy	4-(trifluoromethoxy)phenyl	402	2,3-dimethylphenoxy	2-(methylthio)pyridin-3-yl	365
2,3-dimethylphenoxy	2-fluoro-4-(trifluoromethyl)phenyl	404	2,3-dimethylphenoxy	5-methyl-3-phenylisoxazol-4-yl	399
2,3-dimethylphenoxy	3-bromothienyl	403	2,3-dimethylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	422
2,3-dimethylphenoxy	2-acetoxyphenyl	376	2,3-dimethylphenoxy	2-chloro-6-methylpyridin-4-yl	368
2,3-dimethylphenoxy	5-methylisoxazol-3-yl	323			
2,3-dimethylphenoxy	2-(phenylthio)pyrid-3-yl	427			
2,3-dimethylphenoxy	2-(trifluoromethoxy)phenyl	402			

117

2,3-dimethylphenoxy	3,5-dimethylisoxazol-4-yl	337	2,3-dimethylphenoxy	2,3-dimethylphenoxy	118
2,3-dimethylphenoxy	1-naphthyl	368	2,3-dimethylphenoxy	2-bromophenyl	348
2,3-dimethylphenoxy	2-fluorophenyl	336	2,3-dimethylphenoxy	4-bromophenyl	397
2,3-dimethylphenoxy	4-propylphenyl	360	2,3-dimethylphenoxy	4-fluoro-3-(trifluoromethyl)phenyl	397
2,3-dimethylphenoxy	3-fluorophenyl	336	2,3-dimethylphenoxy	3-(trifluoromethoxy)phenyl	404
2,3-dimethylphenoxy	2,6-difluorophenyl	354	2,3-dimethylphenoxy	9-fluoren-4-yl	402
2,3-dimethylphenoxy	2-chlorophenyl	353	2,3-dimethylphenoxy	isoxazol-5-yl	420
2,3-dimethylphenoxy	3-(chloromethyl)phenyl	368	2,3-dimethylphenoxy	benzofuran-5-yl	609
2,3-dimethylphenoxy	4-(2-(2-methyl)propyl)phenyl	374	2,3-dimethylphenoxy	2-chloropyrid-3-yl	376
2,3-dimethylphenoxy	3-chlorophenyl	353	2,3-dimethylphenoxy	2-(4-methylphenoxy)pyridin-3-yl	354
2,3-dimethylphenoxy	3,5-dimethoxyphenyl	378	2,3-dimethylphenoxy	pyridin-4-yl	425
2,3-dimethylphenoxy	2,6-dichlorophenyl	387	2,3-dimethylphenoxy	anthraquinon-2-yl	319
2,3-dimethylphenoxy	2,4-dichlorophenyl	387	2,3-dimethylphenoxy	2-iodophenyl	448
2,3-dimethylphenoxy	4-fluorophenyl	336	2,3-dimethylphenoxy	4-pentylophenyl	444
2,3-dimethylphenoxy	4-butylphenyl	374	2,3-dimethylphenoxy	2-(4-chlorophenylthio)pyridin-3-yl	388
2,3-dimethylphenoxy	2-methylphenyl	332	2,3-dimethylphenoxy	2,3-dimethylphenox	462
2,3-dimethylphenoxy	phenyl	318	2,3-dimethylphenox	2,3-dimethylphenox	346
2,3-dimethylphenoxy	4-ethylphenyl	346	2,3-dimethylphenox	2,3-dimethylphenox	378
2,3-dimethylphenoxy	2,3-difluorophenyl	354	2,3-dimethylphenox	2,5-dichloropyridin-3-yl	388
2,3-dimethylphenoxy	2,6-dimethoxyphenyl	378	2,3-dimethylphenox	2-chloro-6-methoxypyridin-4-yl	384
2,3-dimethylphenoxy	3,4-difluorophenyl	354	2,3-dimethylphenox	2,3-dichloropyridin-5-yl	388
2,3-dimethylphenoxy	2,5-difluorophenyl	354	2,3-dimethylphenox	1-naphthyl	382
2,3-dimethylphenoxy	4-ethoxyphenyl	362	2,3-dimethylphenox	2,4-dimethoxyphenyl	378
2,3-dimethylphenoxy	2,4,6-trichlorophenyl	422	2,3-dimethylphenox	3-bis(trifluoromethyl)phenyl	454
2,3-dimethylphenoxy	3-methylphenyl	332	2,3-dimethylphenox	2,3-dimethylphenox	404
2,3-dimethylphenoxy	2-fluoro-5-(trifluoromethyl)phenyl				

119

120

2,3-dimethylphenoxy	2-(4-chlorophenoxy)pyridin-3-yl	446	3,5-(bis-2-propyl)phenoxy	2-fluoro-4-(trifluoromethyl)phenyl	460
2,3-dimethylphenoxy	pentfluorophenyl	408	3,5-(bis-2-propyl)phenoxy	3-bromothienyl	459
3,5-(bis-2-propyl)phenoxy	3,4-dimethoxyphenyl	434	3,5-(bis-2-propyl)phenoxy	2-acetoxyphenyl	432
3,5-(bis-2-propyl)phenoxy	2-(trifluoromethyl)phenyl	442	3,5-(bis-2-propyl)phenoxy	5-methylisoxazol-3-yl	379
3,5-(bis-2-propyl)phenoxy	2,4-difluorophenyl	410	3,5-(bis-2-propyl)phenoxy	2-(phenylthio)pyrid-3-yl	484
3,5-(bis-2-propyl)phenoxy	3-(trifluoromethyl)phenyl	442	3,5-(bis-2-propyl)phenoxy	2-(trifluoromethoxy)phenyl	458
3,5-(bis-2-propyl)phenoxy	2-naphthyl	425	3,5-(bis-2-propyl)phenoxy	1-phenyl-5-propylpyrazin-4-yl	483
3,5-(bis-2-propyl)phenoxy	2-methoxyphenyl	404	3,5-(bis-2-propyl)phenoxy	2-ethoxyphenyl	418
3,5-(bis-2-propyl)phenoxy	3,4,5-trimethylphenyl	465	3,5-(bis-2-propyl)phenoxy	3-chlorothiophen-2-yl	415
3,5-(bis-2-propyl)phenoxy	3,4-dichlorophenyl	443	3,5-(bis-2-propyl)phenoxy	1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl	435
3,5-(bis-2-propyl)phenoxy	3-bromophenyl	453	3,5-(bis-2-propyl)phenoxy	3,5-dichlorophenyl	443
3,5-(bis-2-propyl)phenoxy	3-pyridyl	375	3,5-(bis-2-propyl)phenoxy	2-(propylthio)pyridin-3-yl	450
3,5-(bis-2-propyl)phenoxy	2-ethoxynaphth-1-yl	469	3,5-(bis-2-propyl)phenoxy	2-(ethylthio)pyridin-3-yl	436
3,5-(bis-2-propyl)phenoxy	2,3-dichlorophenyl	443	3,5-(bis-2-propyl)phenoxy	3-bromopyridin-5-yl	454
3,5-(bis-2-propyl)phenoxy	6-chloropyrid-3-yl	410	3,5-(bis-2-propyl)phenoxy	4-methyl-1,2,3-thiadiazol-5-yl	396
3,5-(bis-2-propyl)phenoxy	4-(trifluoromethoxy)phenyl	458	3,5-(bis-2-propyl)phenoxy	1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl	435

121

3, 5- (bis-2- propyl) phenoxy	3-chlorobenzo [b] thiophen- 2-yl	465	3, 5- (bis-2- propyl) phenoxy	2, 6-difluorophenyl	410
3, 5- (bis-2- propyl) phenoxy	4-chlorophenyl	409	3, 5- (bis-2- propyl) phenoxy	2-chlorophenyl	409
3, 5- (bis-2- propyl) phenoxy	4-methyl-2-phenyl-1, 2, 3- triazol-5-yl	456	3, 5- (bis-2- propyl) phenoxy	3- (chloromethyl) phenyl	423
3, 5- (bis-2- propyl) phenoxy	benzo [b] thiophen-2-yl	431	3, 5- (bis-2- propyl) phenoxy	4- (2- (2-methyl) propyl) phenyl	431
3, 5- (bis-2- propyl) phenoxy	3, 4-dimethylphenyl	402	3, 5- (bis-2- propyl) phenoxy	3-chlorophenyl	409
3, 5- (bis-2- propyl) phenoxy	2-(phenoxo) pyridin-3-yl	468	3, 5- (bis-2- propyl) phenoxy	3, 5-dimethoxyphenyl	434
3, 5- (bis-2- propyl) phenoxy	2-(methylthio) pyridin-3-yl	422	3, 5- (bis-2- propyl) phenoxy	2, 6-dichlorophenyl	443
3, 5- (bis-2- propyl) phenoxy	5-methyl-1-3-phenylisoxazol- 4-yl	456	3, 5- (bis-2- propyl) phenoxy	2, 4-dichlorophenyl	443
3, 5- (bis-2- propyl) phenoxy	4-chloro-1, 3-dimethyl pyrazolo [3, 4-b] pyridin-3- yl	478	3, 5- (bis-2- propyl) phenoxy	3, 5- (bis-2- propyl) phenoxy	392
3, 5- (bis-2- propyl) phenoxy	2-chloro-6-methylpyridin- 4-yl	424	3, 5- (bis-2- propyl) phenoxy	4-fluorophenyl	431
3, 5- (bis-2- propyl) phenoxy	3, 5-dimethylisoxazol-4-yl	393	3, 5- (bis-2- propyl) phenoxy	4-butylphenyl	402
3, 5- (bis-2- propyl) phenoxy	1-naphthyl	425	3, 5- (bis-2- propyl) phenoxy	2-methylphenyl	388
3, 5- (bis-2- propyl) phenoxy	2-fluorophenyl	392	3, 5- (bis-2- propyl) phenoxy	phenyl	374
3, 5- (bis-2- propyl) phenoxy	4-propylphenyl	417	3, 5- (bis-2- propyl) phenoxy	4-ethylphenyl	402
3, 5- (bis-2- propyl) phenoxy	3-fluorophenyl	392	3, 5- (bis-2- propyl) phenoxy	2, 3-difluorophenyl	410
3, 5- (bis-2- propyl) phenoxy			3, 5- (bis-2- propyl) phenoxy	2, 6-dimethoxyphenyl	434

123

3,5-(bis-2-propyl)phenoxy	3,4-difluorophenyl	410	3,5-(bis-2-propyl)phenoxy	2-(4-methylphenoxy)pyridin-3-yl	482
3,5-(bis-2-propyl)phenoxy	2,5-difluorophenyl	410	3,5-(bis-2-propyl)phenoxy	pyridin-4-yl	375
3,5-(bis-2-propyl)phenoxy	4-ethoxyphenyl	418	3,5-(bis-2-propyl)phenoxy	anthraquinon-2-yl	505
3,5-(bis-2-propyl)phenoxy	2,4,6-trichlorophenyl	478	3,5-(bis-2-propyl)phenoxy	2-iodophenyl	500
3,5-(bis-2-propyl)phenoxy	3-methylphenyl	388	3,5-(bis-2-propyl)phenoxy	4-pentylphenyl	445
3,5-(bis-2-propyl)phenoxy	2-fluoro-5-(trifluoromethyl)phenyl	460	3,5-(bis-2-propyl)phenoxy	2-(4-chlorophenylthio)pyridin-3-yl	518
3,5-(bis-2-propyl)phenoxy	3-methoxyphenyl	404	3,5-(bis-2-propyl)phenoxy	2,6-dimethylphenyl	402
3,5-(bis-2-propyl)phenoxy	2-bromophenyl	453	3,5-(bis-2-propyl)phenoxy	2,5-dimethoxyphenyl	434
3,5-(bis-2-propyl)phenoxy	4-bromophenyl	453	3,5-(bis-2-propyl)phenoxy	2,5-dichloropyridin-3-yl	444
3,5-(bis-2-propyl)phenoxy	4-fluoro-3-(trifluoromethyl)phenyl	460	3,5-(bis-2-propyl)phenoxy	2-chloro-6-methoxypyridin-4-yl	440
3,5-(bis-2-propyl)phenoxy	3-(trifluoromethoxy)phenyl	458	3,5-(bis-2-propyl)phenoxy	2,3-dichloropyridin-5-yl	444
3,5-(bis-2-propyl)phenoxy	9-fluorenon-4-yl	477	3,5-(bis-2-propyl)phenoxy	1-naphthyl	439
3,5-(bis-2-propyl)phenoxy	1isoxazol-5-yl	365	3,5-(bis-2-propyl)phenoxy	2,4-dimethoxyphenyl	434
3,5-(bis-2-propyl)phenoxy	benzofuran-5-yl	432	3,5-(bis-2-propyl)phenoxy	3,5-bis(trifluoromethyl)phenyl	510
3,5-(bis-2-propyl)phenoxy	2-chloropyrid-3-yl	410	3,5-(bis-2-propyl)phenoxy	2-(4-chlorophenoxy)pyridin-3-yl	502

125

3,5-(bis-2- propyl)phenoxy	464	pentafluorophenyl	444
3-trifluoromethyl phenoxy	418	3,4-dimethoxyphenyl	443
3-trifluoromethyl phenoxy	426	2-(trifluoromethyl)phenyl	416
3-trifluoromethyl phenoxy	394	2,4-difluorophenyl	363
3-trifluoromethyl phenoxy	426	3-(trifluoromethyl)phenyl	467
3-trifluoromethyl phenoxy	408	2-naphthyl	442
3-trifluoromethyl phenoxy	388	2-methoxyphenyl	466
3-trifluoromethyl phenoxy	448	3,4,5-trimethylphenyl	402
3-trifluoromethyl phenoxy	427	3,4-dichlorophenyl	399
3-trifluoromethyl phenoxy	437	3-bromophenyl	418
3-trifluoromethyl phenoxy	359	3-pyridyl	427
3-trifluoromethyl phenoxy	452	2-ethoxynaphth-1-yl	433
3-trifluoromethyl phenoxy	427	2,3-dichlorophenyl	419
3-trifluoromethyl phenoxy	394	6-chloropyrid-3-yl	438
3-trifluoromethyl phenoxy	442	4-(trifluoromethoxy)phenyl	380

126

3-trifluoromethyl phenoxy	444	2-fluoro-4-(trifluoromethyl)phenyl	444
3-trifluoromethyl phenoxy	418	3-bromophenyl	443
3-trifluoromethyl phenoxy	426	2-acetoxypyhenyl	416
3-trifluoromethyl phenoxy	394	5-methylisoxazol-3-yl	363
3-trifluoromethyl phenoxy	426	2-(phenylthio)pyrid-3-yl	467
3-trifluoromethyl phenoxy	408	2-(trifluoromethoxy)phenyl	442
3-trifluoromethyl phenoxy	388	1-phenyl-5-propylpyrazin-4-yl	466
3-trifluoromethyl phenoxy	448	2-ethoxyphenyl	402
3-trifluoromethyl phenoxy	427	3-chlorothien-2-yl	399
3-trifluoromethyl phenoxy	437	3-trifluoromethyl	418
3-trifluoromethyl phenoxy	359	1-(2-(2-methyl)propyl)pyrid-3-yl	419
3-trifluoromethyl phenoxy	452	3,5-dichlorophenyl	427
3-trifluoromethyl phenoxy	427	3-trifluoromethyl	433
3-trifluoromethyl phenoxy	394	2-(ethylthio)pyridin-3-yl	419
3-trifluoromethyl phenoxy	442	3-trifluoromethyl	438
3-trifluoromethyl phenoxy	380	4-methyl-1,2,3-thiadiazol-5-yl	380

127

3-trifluoromethyl phenoxy	1-methyl-3-(2-(2- methyl)propyl)pyrazol-5-yl	418	3-trifluoromethyl phenoxy	3-fluorophenyl	376
3-trifluoromethyl phenoxy	3-chlorobenzothiophen- 2-yl	449	3-trifluoromethyl phenoxy	2,6-difluorophenyl	394
3-trifluoromethyl phenoxy	4-chlorophenyl	393	3-trifluoromethyl phenoxy	2-chlorophenyl	393
3-trifluoromethyl phenoxy	4-methyl-2-phenyl-1,2,3- triazol-5-yl	439	3-trifluoromethyl phenoxy	3-(chloromethyl)phenyl	407
3-trifluoromethyl phenoxy	benzo[b]thiophen-2-yl	414	3-trifluoromethyl phenoxy	4-(2-(2-methyl)propyl) phenyl	414
3-trifluoromethyl phenoxy	3,4-dimethylphenyl	386	3-trifluoromethyl phenoxy	3-chlorophenyl	393
3-trifluoromethyl phenoxy	2-(phenoxy)pyridin-3-yl	451	3-trifluoromethyl phenoxy	3,5-dimethoxyphenyl	418
3-trifluoromethyl phenoxy	2-(methylthio)pyridin-3-yl	405	3-trifluoromethyl phenoxy	2,6-dichlorophenyl	427
3-trifluoromethyl phenoxy	4-yl	439	3-trifluoromethyl phenoxy	2,4-dichlorophenyl	427
3-trifluoromethyl phenoxy	5-methyl-3-phenylisoxazol- 4-yl	462	3-trifluoromethyl phenoxy	4-fluorophenyl	376
3-trifluoromethyl phenoxy	4-chloro-1,3-dimethyl pyrazolo[3,4-b]pyridin-3- yl	462	3-trifluoromethyl phenoxy	4-hutylphenyl	414
3-trifluoromethyl phenoxy	2-chloro-6-methylpyridin- 4-yl	408	3-trifluoromethyl phenoxy	2-methylphenyl	372
3-trifluoromethyl phenoxy	3,5-dimethylisoxazol-4-yl	377	3-trifluoromethyl phenoxy	phenyl	358
3-trifluoromethyl phenoxy	1-naphthyl	408	3-trifluoromethyl phenoxy	4-ethylphenyl	386
3-trifluoromethyl phenoxy	2-fluorophenyl	476	3-trifluoromethyl phenoxy	2,3-difluorophenyl	394
3-trifluoromethyl phenoxy	4-propylphenyl	400	3-trifluoromethyl phenoxy	2,6-dimethoxyphenyl	418

3-trifluoromethyl phenoxy	3,4-difluorophenyl	129	3-trifluoromethyl phenoxy	pyridin-4-yl	130	3-trifluoromethyl phenoxy	pyridin-4-yl	359	
3-trifluoromethyl phenoxy	2,5-difluorophenyl	394	3-trifluoromethyl phenoxy	anthraquinon-2-yl	488	3-trifluoromethyl phenoxy	2-iodophenyl	484	
3-trifluoromethyl phenoxy	4-ethoxyphenyl	402	3-trifluoromethyl phenoxy	4-trifluoromethyl	428	3-trifluoromethyl phenoxy	4-pentylophenyl	428	
3-trifluoromethyl phenoxy	2,4,6-trichlorophenyl	462	3-trifluoromethyl phenoxy	2-(4-chlorophenylthio)	502	3-trifluoromethyl phenoxy	2-(4-chlorophenyl)	502	
3-trifluoromethyl phenoxy	3-methylphenyl	372	3-trifluoromethyl phenoxy	pyridin-3-yl	386	3-trifluoromethyl phenoxy	2,6-dimethylphenyl	386	
3-trifluoromethyl phenoxy	2-fluoro-5-(trifluoromethyl)phenyl	444	3-trifluoromethyl phenoxy	2,5-dimethoxyphenyl	418	3-trifluoromethyl phenoxy	2,5-dimethoxyphenyl	418	
3-trifluoromethyl phenoxy	3-methoxyphenyl	388	3-trifluoromethyl phenoxy	2,5-dichloropyridin-3-yl	428	3-trifluoromethyl phenoxy	2,5-dichloropyridin-3-yl	428	
3-trifluoromethyl phenoxy	2-bromophenyl	437	3-trifluoromethyl phenoxy	2-chloro-6-methoxypyridin-4-yl	424	3-trifluoromethyl phenoxy	2,3-dichloropyridin-5-yl	428	
3-trifluoromethyl phenoxy	4-bromophenyl	437	3-trifluoromethyl phenoxy	3-trifluoromethyl	422	3-trifluoromethyl phenoxy	1-naphthyl	422	
3-trifluoromethyl phenoxy	4-fluoro-3-(trifluoromethyl)phenyl	444	3-trifluoromethyl phenoxy	2,4-dimethoxyphenyl	418	3-trifluoromethyl phenoxy	2,4-dimethoxyphenyl	418	
3-trifluoromethyl phenoxy	3-(trifluoromethoxy)phenyl	442	3-trifluoromethyl phenoxy	3,5-bis(trifluoromethyl)phenyl	494	3-trifluoromethyl phenoxy	3,5-bis(trifluoromethyl)phenyl	494	
3-trifluoromethyl phenoxy	9-fluoren-4-yl	460	3-trifluoromethyl phenoxy	2-(4-chlorophenoxy)pyridin-3-yl	486	3-trifluoromethyl phenoxy	2-(4-chlorophenoxy)pyridin-3-yl	486	
3-trifluoromethyl phenoxy	isoxazol-5-yl	349	3-trifluoromethyl phenoxy	5-pentafluorophenyl	448	3-trifluoromethyl phenoxy	2,6-dimethoxyphenyl	448	
3-trifluoromethyl phenoxy	benzofuran-5-yl	416	3-trifluoromethyl phenoxy	3,4-dimethoxyphenyl	419	3-trifluoromethyl phenoxy	3,4-dimethoxyphenyl	419	
3-trifluoromethyl phenoxy	2-chloropyridin-3-yl	394							
3-trifluoromethyl phenoxy	2-(4-methylphenoxy)pyridin-3-yl	465							

131

132

2,6-dichlorophenoxy	2-(trifluoromethyl)phenyl	427	2,6-dichlorophenoxy	2-(ethylthio)pyridin-3-yl	420	
2,6-dichlorophenoxy	2,4-difluorophenyl	395	2,6-dichlorophenoxy	3-bromopyridin-5-yl	439	
2,6-dichlorophenoxy	3-(trifluoromethyl)phenyl	427	2,6-dichlorophenoxy	4-methyl-1,2,3-thiadiazol-5-yl	381	
2,6-dichlorophenoxy	2-naphthyl	409	2,6-dichlorophenoxy	1-methyl-3-(2-(2-methylpropyl)pyrazol-5-yl	419	
2,6-dichlorophenoxy	2-methoxyphenyl	389	2,6-dichlorophenoxy	3-chlorobenz[b]thiophen-2-yl	450	
2,6-dichlorophenoxy	3,4,5-trimethylphenyl	449	2,6-dichlorophenoxy	4-chlorophenyl	394	
2,6-dichlorophenoxy	3,4-dichlorophenyl	428	2,6-dichlorophenoxy	4-methyl-1,2-phenyl-triazol-5-yl	440	
2,6-dichlorophenoxy	3-bromophenyl	438	2,6-dichlorophenoxy	benzo[b]thiophen-2-yl	415	
2,6-dichlorophenoxy	3-pyridyl	361	2,6-dichlorophenoxy	3,4-dimethylphenyl	387	
2,6-dichlorophenoxy	2-ethoxynaphth-1-yl	453	2,6-dichlorophenoxy	2-(phenoxy)pyridin-3-yl	452	
2,6-dichlorophenoxy	2,3-dichlorophenyl	428	2,6-dichlorophenoxy	2-(trifluoromethyl)phenyl	406	
2,6-dichlorophenoxy	6-chloropyrid-3-yl	395	2,6-dichlorophenoxy	5-methyl-3-phenylisoxazol-4-yl	440	
2,6-dichlorophenoxy	4-(trifluoromethoxy)phenyl	443	2,6-dichlorophenoxy	4-chloro-1,3-dimethylpyrazol-4-yl	463	
2,6-dichlorophenoxy	2-fluoro-4-(trifluoromethyl)phenyl	445	2,6-dichlorophenoxy	4-methyl-3-phenylisoxazol-5-yl	440	
2,6-dichlorophenoxy	3-bromobenyl	444	2,6-dichlorophenoxy	2-(methylthio)pyridin-3-yl	406	
2,6-dichlorophenoxy	2-acetoxyphenyl	417	2,6-dichlorophenoxy	2-chloro-6-methylpyridin-4-yl	409	
2,6-dichlorophenoxy	5-methylisoxazol-3-yl	364	2,6-dichlorophenoxy	3,5-dimethylisoxazol-4-yl	378	
2,6-dichlorophenoxy	2-(phenylthiopyrid-3-yl	468	2,6-dichlorophenoxy	1-naphthyl	409	
2,6-dichlorophenoxy	2-(trifluoromethoxy)phenyl	443	2,6-dichlorophenoxy	2-fluorophenyl	377	
2,6-dichlorophenoxy	1-phenyl-5-propylpyrazin-4-yl	467	2,6-dichlorophenoxy	4-propylphenyl	401	
2,6-dichlorophenoxy	2-ethoxyphenyl	403	2,6-dichlorophenoxy	2,6-dichlorophenoxy	3-fluorophenyl	377
2,6-dichlorophenoxy	3-chlorothien-2-yl	400	2,6-dichlorophenoxy	2,6-difluorophenyl	395	
2,6-dichlorophenoxy	1-(2-(2-methylpropyl)propyl)-3-methylpyrazol-5-yl	419	2,6-dichlorophenoxy	2-chlorophenyl	394	
2,6-dichlorophenoxy	3,5-dichlorophenyl	428	2,6-dichlorophenoxy	3-(chloromethyl)phenyl	408	
2,6-dichlorophenoxy	2-(propylthiopyridin-3-yl	434				

133

2,6-dichlorophenoxy	4-(2-(2-methyl)propyl)phenyl	415	133
2,6-dichlorophenoxy	3-chlorophenyl	694	2,6-dichlorophenoxy
2,6-dichlorophenoxy	3,5-dimethoxyphenyl	419	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2,6-dichlorophenyl	428	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2,4-dichlorophenyl	428	2,6-dichlorophenoxy
2,6-dichlorophenoxy	4-fluorophenyl	377	2,6-dichlorophenoxy
2,6-dichlorophenoxy	4-butylphenyl	415	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2-methylphenyl	373	2,6-dichlorophenoxy
2,6-dichlorophenoxy	phenyl	359	2,6-dichlorophenoxy
2,6-dichlorophenoxy	4-ethylphenyl	387	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2,3-difluorophenyl	395	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2,6-dimethoxyphenyl	419	2,6-dichlorophenoxy
2,6-dichlorophenoxy	3,4-difluorophenyl	395	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2,5-difluorophenyl	395	2,6-dichlorophenoxy
2,6-dichlorophenoxy	4-ethoxyphenyl	403	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2,4,6-trichlorophenyl	463	2,6-dichlorophenoxy
2,6-dichlorophenoxy	3-methylphenyl	373	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2-fluoro-5-(trifluoromethyl)phenyl	445	2,6-dichlorophenoxy
2,6-dichlorophenoxy	3-methoxyphenyl	389	2,6-dichlorophenoxy
2,6-dichlorophenoxy	2-bromophenyl	438	2,6-dichlorophenoxy
2,6-dichlorophenoxy	4-bromophenyl	438	2,4-dichlorophenoxy
2,6-dichlorophenoxy	4-fluoro-3-(trifluoromethyl)phenyl	445	2,4-dichlorophenoxy
2,6-dichlorophenoxy	3-(trifluoromethoxy)phenyl	443	2,4-dichlorophenoxy
2,6-dichlorophenoxy	9-fluoranon-4-yl	461	2,4-dichlorophenoxy
2,6-dichlorophenoxy	isoxazol-5-yl	350	2,4-dichlorophenoxy

134

2,6-dichlorophenoxy	2,6-dichlorophenoxy	417	benzofuroxan-5-yl
2,6-dichlorophenoxy	2,6-dichlorophenoxy	395	2-chloropyrid-3-yl
2,6-dichlorophenoxy	2-(4-methylphenoxy)pyridin-3-yl	466	2-(4-methylphenoxy)pyridin-3-yl
2,6-dichlorophenoxy	pyridin-4-yl	360	pyridin-4-yl
2,6-dichlorophenoxy	anthraquinon-2-yl	489	anthraquinon-2-yl
2,6-dichlorophenoxy	2-iodophenyl	485	2-iodophenyl
2,6-dichlorophenoxy	4-pentylophenyl	429	4-pentylophenyl
2,6-dichlorophenoxy	2-(4-chlorophenylthio)pyridin-3-yl	503	2-(4-chlorophenylthio)pyridin-3-yl
2,6-dichlorophenoxy	2,6-dimethylphenyl	387	2,6-dimethylphenyl
2,6-dichlorophenoxy	2,5-dimethoxyphenyl	419	2,5-dimethoxyphenyl
2,6-dichlorophenoxy	2,5-dichloropyridin-3-yl	429	2,5-dichloropyridin-3-yl
2,6-dichlorophenoxy	2-chloro-6-methoxypyridin-4-yl	425	2-chloro-6-methoxypyridin-4-yl
2,6-dichlorophenoxy	2,3-dichloropyridin-5-yl	429	2,3-dichloropyridin-5-yl
2,6-dichlorophenoxy	1-naphthyl	413	1-naphthyl
2,6-dichlorophenoxy	2,4-dimethoxyphenyl	419	2,4-dimethoxyphenyl
2,6-dichlorophenoxy	3,5-bis(trifluoromethyl)phenyl	495	3,5-bis(trifluoromethyl)phenyl
2,6-dichlorophenoxy	2-(4-chlorophenoxy)pyridin-3-yl	487	2-(4-chlorophenoxy)pyridin-3-yl
2,6-dichlorophenoxy	pentafluorophenyl	449	pentafluorophenyl
2,6-dichlorophenoxy	3,4-dimethoxyphenyl	419	3,4-dimethoxyphenyl
2,6-dichlorophenoxy	2-(trifluoromethyl)phenyl	427	2-(trifluoromethyl)phenyl
2,6-dichlorophenoxy	2,4-difluorophenyl	395	2,4-difluorophenyl
2,6-dichlorophenoxy	3-(trifluoromethyl)phenyl	427	3-(trifluoromethyl)phenyl
2,6-dichlorophenoxy	2-naphthyl	409	2-naphthyl
2,6-dichlorophenoxy	2-methoxyphenyl	389	2-methoxyphenyl

135

2,4-dichlorophenoxy	3,4,5-trimethylphenyl	449	2,4-dichlorophenoxy	3-chlorobenzo[b]thiophen-2-yl	450
2,4-dichlorophenoxy	3,4-dichlorophenyl	428	2,4-dichlorophenoxy	4-chlorophenyl	394
2,4-dichlorophenoxy	3-bromophenyl	438	2,4-dichlorophenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	440
2,4-dichlorophenoxy	3-pyridyl	361	2,4-dichlorophenoxy	benzo[b]thiophen-2-yl	415
2,4-dichlorophenoxy	2-ethoxynaphth-1-yl	453	2,4-dichlorophenoxy	2,4-dichlorophenyl	387
2,4-dichlorophenoxy	2,3-dichlorophenyl	428	2,4-dichlorophenoxy	3,4-dimethylphenyl	452
2,4-dichlorophenoxy	6-chloropyrid-3-yl	395	2,4-dichlorophenoxy	2-(phenoxyl)pyridin-3-yl	406
2,4-dichlorophenoxy	4-(trifluoromethoxy)phenyl	443	2,4-dichlorophenoxy	2-(methylthio)pyridin-3-yl	406
2,4-dichlorophenoxy	2-fluoro-4-(trifluoromethyl)phenyl	445	2,4-dichlorophenoxy	5-methyl-3-phenylisoxazol-4-yl	440
2,4-dichlorophenoxy	3-bromothienyl	444	2,4-dichlorophenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	463
2,4-dichlorophenoxy	2-acetoxyphenyl	417	2,4-dichlorophenoxy	2-chloro-6-methylpyridin-4-yl	409
2,4-dichlorophenoxy	5-methylisoxazol-3-yl	364	2,4-dichlorophenoxy	3,5-dimethylisoxazol-4-yl	378
2,4-dichlorophenoxy	2-(phenylthio)pyrid-3-yl	468	2,4-dichlorophenoxy	1-naphthyl	409
2,4-dichlorophenoxy	2-(trifluoromethoxy)phenyl	443	2,4-dichlorophenoxy	2-fluorophenyl	377
2,4-dichlorophenoxy	1-phenyl-5-propylpyrazin-4-yl	467	2,4-dichlorophenoxy	4-propylphenyl	401
2,4-dichlorophenoxy	2-ethoxyphenyl	403	2,4-dichlorophenoxy	3-fluorophenyl	377
2,4-dichlorophenoxy	3-chlorothien-2-yl	400	2,4-dichlorophenoxy	2,6-difluorophenyl	395
2,4-dichlorophenoxy	1-(2-(2-methylpropyl)-5-methylpyrazol-5-yl	419	2,4-dichlorophenoxy	2-chlorophenyl	394
2,4-dichlorophenoxy	3,5-dichlorophenyl	428	2,4-dichlorophenoxy	3-(chloromethyl)phenyl	408
2,4-dichlorophenoxy	2-(propylthio)pyridin-3-yl	434	2,4-dichlorophenoxy	4-(2-(methylpropyl)phenyl	415
2,4-dichlorophenoxy	2-(ethylthio)pyridin-3-yl	420	2,4-dichlorophenoxy	3-chlorophenyl	694
2,4-dichlorophenoxy	3-bromopyridin-5-yl	439	2,4-dichlorophenoxy	3,5-dimethoxyphenyl	419
2,4-dichlorophenoxy	4-methyl-1,2,3-thiadiazol-5-yl	381	2,4-dichlorophenoxy	2,6-dichlorophenyl	428
2,4-dichlorophenoxy	1-methyl-1-(2-(2-methylpropyl)pyrazol-5-yl	419			

136

2,4-dichlorophenoxy	3-chlorobenzo[b]thiophen-2-yl	450
2,4-dichlorophenoxy	4-chlorophenyl	394
2,4-dichlorophenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	440
2,4-dichlorophenoxy	benzo[b]thiophen-2-yl	415
2,4-dichlorophenoxy	2,4-dichlorophenyl	387
2,4-dichlorophenoxy	3,4-dimethylphenyl	452
2,4-dichlorophenoxy	2-(phenoxyl)pyridin-3-yl	406
2,4-dichlorophenoxy	2-(methylthio)pyridin-3-yl	406
2,4-dichlorophenoxy	5-methyl-3-phenylisoxazol-4-yl	440
2,4-dichlorophenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	463
2,4-dichlorophenoxy	2-chloro-6-methylpyridin-4-yl	409
2,4-dichlorophenoxy	3,5-dimethylisoxazol-4-yl	378
2,4-dichlorophenoxy	1-naphthyl	409
2,4-dichlorophenoxy	2-fluorophenyl	377
2,4-dichlorophenoxy	4-propylphenyl	401
2,4-dichlorophenoxy	3-fluorophenyl	377
2,4-dichlorophenoxy	2,6-difluorophenyl	395
2,4-dichlorophenoxy	2-chlorophenyl	394
2,4-dichlorophenoxy	3-(chloromethyl)phenyl	408
2,4-dichlorophenoxy	4-(2-(methylpropyl)phenyl	415
2,4-dichlorophenoxy	3-chlorophenyl	694
2,4-dichlorophenoxy	3,5-dimethoxyphenyl	419
2,4-dichlorophenoxy	2,6-dichlorophenyl	428

137

2,4-dichlorophenoxy	2,4-dichlorophenyl	428
2,4-dichlorophenoxy	4-fluorophenyl	377
2,4-dichlorophenoxy	4-butylophenyl	415
2,4-dichlorophenoxy	2-methyllophenyl	373
2,4-dichlorophenoxy	phenyl	359
2,4-dichlorophenoxy	4-ethylphenyl	387
2,4-dichlorophenoxy	2,3-difluorophenyl	395
2,4-dichlorophenoxy	2,6-dimethoxyphenyl	419
2,4-dichlorophenoxy	3,4-difluorophenyl	395
2,4-dichlorophenoxy	2,5-difluorophenyl	395
2,4-dichlorophenoxy	4-ethoxyphenyl	403
2,4-dichlorophenoxy	2,4,6-trichlorophenyl	463
2,4-dichlorophenoxy	3-methylphenyl	373
2,4-dichlorophenoxy	2-fluoro-5-(trifluoromethyl)phenyl	445
2,4-dichlorophenoxy	3-methoxyphenyl	389
2,4-dichlorophenoxy	2-bromophenyl	438
2,4-dichlorophenoxy	4-bromophenyl	438
2,4-dichlorophenoxy	4-fluoro-3-(trifluoromethyl)phenyl	445
2,4-dichlorophenoxy	3-(trifluoromethoxy)phenyl	443
2,4-dichlorophenoxy	9-fluoren-4-yl	461
2,4-dichlorophenoxy	isoxazol-5-yl	350
2,4-dichlorophenoxy	benzoturoean-5-yl	417
2,4-dichlorophenoxy	2-chloropyrid-3-yl	395
2,4-dichlorophenoxy	2-(4-methylphenoxy)pyridin-3-yl	466
2,4-dichlorophenoxy	pyridin-4-yl	360

138

2,4-dichlorophenoxy	anthraquinon-2-yl	489
2,4-dichlorophenoxy	2-iodophenyl	485
2,4-dichlorophenoxy	4-pentylophenyl	429
2,4-dichlorophenoxy	2-(4-chlorophenylthio)pyridin-3-yl	503
2,4-dichlorophenoxy	2,4-dichlorophenoxy	387
2,4-dichlorophenoxy	2,4-dichlorophenoxy	419
2,4-dichlorophenoxy	2,4-dichlorophenoxy	429
2,4-dichlorophenoxy	2,4-dichlorophenoxy	425
2,4-dichlorophenoxy	4-yl	419
2,4-dichlorophenoxy	2,3-dichloropyridin-5-yl	429
2,4-dichlorophenoxy	1-naphthyl	413
2,4-dichlorophenoxy	2,4-dimethoxyphenyl	419
2,4-dichlorophenoxy	3,5-bis(trifluoromethyl)phenyl	495
2,4-dichlorophenoxy	2-(4-chlorophenoxy)pyridin-3-yl	487
2,4-dichlorophenoxy	pentafluorophenyl	449
2,4-dichlorophenoxy	3,4-dimethoxyphenyl	319
2,4-dichlorophenoxy	2-(trifluoromethyl)phenyl	407
2,4-dichlorophenoxy	2,4-difluorophenyl	375
2,4-dichlorophenoxy	3-(trifluoromethyl)phenyl	407
2,4-dichlorophenoxy	4-chloro-3-methylphenoxy	389
2,4-dichlorophenoxy	4-chloro-3-methylphenyl	389
2,4-dichlorophenoxy	4-chloro-3-methylphenyl	389
2,4-dichlorophenoxy	2-naphthyl	389
2,4-dichlorophenoxy	4-chloro-3-methylphenoxy	369

139

140

4-chloro-3-methylphenoxy	3,4,5-trimethylphenyl	429	4-chloro-3-methylphenoxy	3-chlorothien-2-yl	379
4-chloro-3-methylphenoxy	3,4-dichlorophenyl	408	4-chloro-3-methylphenoxy	1-(2-(2-methylpropyl)propyl)-3-methylpyrazol-5-yl	399
4-chloro-3-methylphenoxy	3-bromophenyl	418	4-chloro-3-methylphenoxy	3,5-dichlorophenyl	408
4-chloro-3-methylphenoxy	3-pyridyl	340	4-chloro-3-methylphenoxy	2-(propylthio)pyridin-3-yl	414
4-chloro-3-methylphenoxy	2-ethoxymaphth-1-yl	433	4-chloro-3-methylphenoxy	2-(ethylthio)pyridin-3-yl	400
4-chloro-3-methylphenoxy	2,3-dichlorophenyl	408	4-chloro-3-methylphenoxy	3-bromopyridin-5-yl	419
4-chloro-3-methylphenoxy	6-chloropyrid-3-yl	374	4-chloro-3-methylphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	361
4-chloro-3-methylphenoxy	4-(trifluoromethoxy)phenyl	423	4-chloro-3-methylphenoxy	1-methyl-3-(2-(2-methylpropyl)propyl)pyrazol-5-yl	399
4-chloro-3-methylphenoxy	2-fluoro-4-(trifluoromethyl)phenyl	425	4-chloro-3-methylphenoxy	3-chlorobenzo[b]thiophen-2-yl	429
4-chloro-3-methylphenoxy	3-bromothienyl	424	4-chloro-3-methylphenoxy	4-chlorophenyl	373
4-chloro-3-methylphenoxy	2-acetoxyphenyl	397	4-chloro-3-methylphenoxy	4-methyl-1-2-phenyl-1,2,3-triazol-5-yl	420
4-chloro-3-methylphenoxy	5-methylisoxazol-3-yl	344	4-chloro-3-methylphenoxy	benzo[b]thiophen-2-yl	395
4-chloro-3-methylphenoxy	2-(phenylthio)pyrid-3-yl	448	4-chloro-3-methylphenoxy	3,4-dimethylphenyl	367
4-chloro-3-methylphenoxy	2-(trifluoromethoxy)phenyl	423	4-chloro-3-methylphenoxy	2-(phenoxy)pyridin-3-yl	432
4-chloro-3-methylphenoxy	1-phenyl-5-propylpyrazin-4-yl	447	4-chloro-3-methylphenoxy	2-(methylthio)pyridin-3-yl	386
4-chloro-3-methylphenoxy	2-ethoxyphenyl	383	4-chloro-3-methylphenoxy	5-methyl-3-phenylisoxazol-4-yl	420

141		142	
4-chloro-3-methylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	442	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	2-chloro-6-methylpyridin-4-yl	388	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	3,5-dimethylisoxazol-4-yl	358	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	1-naphthyl	389	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	2-fluorophenyl	357	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	4-propylphenyl	381	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	4-(trifluoromethyl)phenyl	407	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	3-fluorophenyl	357	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	2,6-difluorophenyl	375	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	2-chlorophenyl	373	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	3-(chloromethyl)phenyl	387	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	4-(2-(2-methylpropyl)phenyl	395	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	3-chlorophenyl	373	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	3,5-dimethoxyphenyl	399	4-chloro-3-methylphenoxy
4-chloro-3-methylphenoxy	2,6-dichlorophenyl	408	4-chloro-3-methylphenoxy

143

144

4-chloro-3-methylphenoxy	2-bromophenyl	418	4-chloro-3-methylphenoxy	2,5-dimethoxyphenyl	399
4-chloro-3-methylphenoxy	4-bromophenyl	418	4-chloro-3-methylphenoxy	2,5-dichloropyridin-3-yl	409
4-chloro-3-methylphenoxy	4-fluoro-3-(trifluoromethyl)phenyl	425	4-chloro-3-methylphenoxy	2-chloro-6-methoxypyridin-4-yl	404
4-chloro-3-methylphenoxy	3-(trifluoromethyl)phenyl	423	4-chloro-3-methylphenoxy	2,3-dichloropyridin-5-yl	409
4-chloro-3-methylphenoxy	9-fluoren-4-yl	441	4-chloro-3-methylphenoxy	1-naphthyl	403
4-chloro-3-methylphenoxy	isoxazol-5-yl	330	4-chloro-3-methylphenoxy	2,4-dimethoxyphenyl	399
4-chloro-3-methylphenoxy	benzofuran-5-yl	397	4-chloro-3-methylphenoxy	3,5-bis(trifluoromethyl)phenyl	475
4-chloro-3-methylphenoxy	2-chloropyrid-3-yl	374	4-chloro-3-methylphenoxy	2-(4-chlorophenoxy)pyridin-3-yl	466
4-chloro-3-methylphenoxy	2-(4-methylphenoxy)pyridin-3-yl	446	4-chloro-3-methylphenoxy	perfluorophenyl	429
4-chloro-3-methylphenoxy	pyridin-4-yl	340	4-chloro-2-cyclohexylphenoxy	3,4-dimethoxyphenyl	467
4-chloro-3-methylphenoxy	anthraquinon-2-yl	469	4-chloro-2-cyclohexylphenoxy	2-(trifluoromethyl)phenyl	475
4-chloro-3-methylphenoxy	2-iodophenyl	465	4-chloro-2-cyclohexylphenoxy	2,4-difluorophenyl	443
4-chloro-3-methylphenoxy	4-pentylphenyl	409	4-chloro-2-cyclohexylphenoxy	cyclohexylphenoxy	
4-chloro-3-methylphenoxy	2-(4-chlorophenylthio)pyridin-3-yl	482	4-chloro-2-cyclohexylphenoxy	3-(trifluoromethyl)phenyl	475
4-chloro-3-methylphenoxy	2,6-dimethylphenyl	367	4-chloro-2-cyclohexylphenoxy	2-naphthyl	457
4-chloro-3-methylphenoxy	cyclohexylphenoxy		4-chloro-2-cyclohexylphenoxy	2-methoxyphenyl	437

145

146

4-chloro-2-cyclohexylphenoxy	3,4,5-trimethylphenyl	497	4-chloro-2-cyclohexylphenoxy	2-ethoxyphenyl	451
4-chloro-2-cyclohexylphenoxy	3,4-dichlorophenyl	176	4-chloro-2-cyclohexylphenoxy	3-chlorothien-2-yl	447
4-chloro-2-cyclohexylphenoxy	3-bromophenyl	486	4-chloro-2-cyclohexylphenoxy	1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl	467
4-chloro-2-cyclohexylphenoxy	3-pyridyl	408	4-chloro-2-cyclohexylphenoxy	3,5-dichlorophenyl	476
4-chloro-2-cyclohexylphenoxy	2-ethoxynaphth-1-yl	501	4-chloro-2-cyclohexylphenoxy	2-(propylthio)pyridin-3-yl	482
4-chloro-2-cyclohexylphenoxy	2,3-dichlorophenyl	476	4-chloro-2-cyclohexylphenoxy	2-(ethylthio)pyridin-3-yl	468
4-chloro-2-cyclohexylphenoxy	6-chloropyrid-3-yl	442	4-chloro-2-cyclohexylphenoxy	3-bromopyridin-5-yl	487
4-chloro-2-cyclohexylphenoxy	4-(trifluoromethoxy)phenyl	491	4-chloro-2-cyclohexylphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	429
4-chloro-2-cyclohexylphenoxy	2-fluoro-4-(trifluoromethyl)phenyl	493	4-chloro-2-cyclohexylphenoxy	1-methyl-1-(2-(2-methyl)propyl)pyrazol-5-yl	467
4-chloro-2-cyclohexylphenoxy	3-bromothieryl	492	4-chloro-2-cyclohexylphenoxy	3-chlorobenzo[b]thiophen-2-yl	497
4-chloro-2-cyclohexylphenoxy	2-acetoxyphenyl	465	4-chloro-2-cyclohexylphenoxy	4-chlorophenyl	441
4-chloro-2-cyclohexylphenoxy	5-methylisoxazol-3-yl	412	4-chloro-2-cyclohexylphenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	488
4-chloro-2-cyclohexylphenoxy	2-(phenylthio)pyrid-3-yl	516	4-chloro-2-cyclohexylphenoxy	benzo[b]thiophen-2-yl	463
4-chloro-2-cyclohexylphenoxy	2-(trifluoromethoxy)phenyl	491	4-chloro-2-cyclohexylphenoxy	3,4-dimethylphenyl	435
4-chloro-2-cyclohexylphenoxy	1-phenyl-5-propylpyrazin-4-yl	515	4-chloro-2-cyclohexylphenoxy	2-(phenoxy)pyridin-3-yl	500

147

148

4-chloro-2-cyclohexylphenoxy	2-(methylthio)pyridin-3-yl	454	4-chloro-2-cyclohexylphenoxy	2,6-dichlorophenyl	476
4-chloro-2-cyclohexylphenoxy	5-methyl-3-phenylisoxazol-4-yl	488	4-chloro-2-cyclohexylphenoxy	2,4-dichlorophenyl	476
4-chloro-2-cyclohexylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	510	4-chloro-2-cyclohexylphenoxy	4-fluorophenyl	425
4-chloro-2-cyclohexylphenoxy	2-chloro-6-methylpyridin-4-yl	456	4-chloro-2-cyclohexylphenoxy	4-butylophenyl	463
4-chloro-2-cyclohexylphenoxy	3,5-dimethylisoxazol-4-yl	426	4-chloro-2-cyclohexylphenoxy	2-methylphenyl	421
4-chloro-2-cyclohexylphenoxy	1-naphthyl	457	4-chloro-2-cyclohexylphenoxy	4-ethylphenyl	435
4-chloro-2-cyclohexylphenoxy	2-fluorophenyl	425	4-chloro-2-cyclohexylphenoxy	2,3-difluorophenyl	443
4-chloro-2-cyclohexylphenoxy	4-propylphenyl	449	4-chloro-2-cyclohexylphenoxy	2,6-dimethoxyphenyl	467
4-chloro-2-cyclohexylphenoxy	3-fluorophenyl	425	4-chloro-2-cyclohexylphenoxy	3,4-difluorophenyl	443
4-chloro-2-cyclohexylphenoxy	2,6-difluorophenyl	443	4-chloro-2-cyclohexylphenoxy	2,5-difluorophenyl	443
4-chloro-2-cyclohexylphenoxy	2-chlorophenyl	441	4-chloro-2-cyclohexylphenoxy	4-ethoxyphenyl	451
4-chloro-2-cyclohexylphenoxy	3-(chloromethyl)phenyl	455	4-chloro-2-cyclohexylphenoxy	2,4,6-trichlorophenyl	510
4-chloro-2-cyclohexylphenoxy	4-(2-(2-methyl)propyl)phenyl	463	4-chloro-2-cyclohexylphenoxy	3-methylphenyl	421
4-chloro-2-cyclohexylphenoxy	3-chlorophenyl	441	4-chloro-2-cyclohexylphenoxy	2-fluoro-5-(trifluoromethyl)phenyl	493
4-chloro-2-cyclohexylphenoxy	3,5-dimethoxyphenyl	467	4-chloro-2-cyclohexylphenoxy	3-methoxyphenyl	417

149	2-bromophenyl	486	4-chloro-2-cyclohexylphenoxy	149	2,5-dichloropyridin-3-yl	477
4-chloro-2-cyclohexylphenoxy	4-bromophenyl	486	4-chloro-2-cyclohexylphenoxy	486	2-chloro-6-methoxy-4-yl	472
4-chloro-2-cyclohexylphenoxy	4-fluoro-3-(trifluoromethyl)phenyl	493	4-chloro-2-cyclohexylphenoxy	493	2,3-dichloropyridin-5-yl	477
4-chloro-2-cyclohexylphenoxy	3-(trifluoromethoxy)phenyl	491	4-chloro-2-cyclohexylphenoxy	491	1-naphthyl	471
4-chloro-2-cyclohexylphenoxy	9-fluoren-4-yl	503	4-chloro-2-cyclohexylphenoxy	503	2,4-dimethoxyphenyl	467
4-chloro-2-cyclohexylphenoxy	isoxazol-5-yl	398	4-chloro-2-cyclohexylphenoxy	398	3,5-bis(trifluoromethyl)phenyl	546
4-chloro-2-cyclohexylphenoxy	benzofuran-5-yl	465	4-chloro-2-cyclohexylphenoxy	465	2-(4-chlorophenoxy)pyridin-3-yl	534
4-chloro-2-cyclohexylphenoxy	2-chloropyrid-3-yl	442	4-chloro-2-cyclohexylphenoxy	442	pentfluorophenyl	497
4-chloro-2-cyclohexylphenoxy	2-(4-methylphenoxy)pyridin-3-yl	514	4-chloro-3,5-dimethylphenoxy	514	3,4-dimethoxyphenyl	413
4-chloro-2-cyclohexylphenoxy	pyridin-4-yl	408	4-chloro-3,5-dimethylphenoxy	408	2-(trifluoromethyl)phenyl	421
4-chloro-2-cyclohexylphenoxy	anthraquinon-2-yl	537	4-chloro-3,5-dimethylphenoxy	537	2,4-difluorophenyl	389
4-chloro-2-cyclohexylphenoxy	2-iodophenyl	533	4-chloro-3,5-dimethylphenoxy	533	3-(trifluoromethyl)phenyl	421
4-chloro-2-cyclohexylphenoxy	4-pentylphenyl	477	4-chloro-3,5-dimethylphenoxy	477	2-naphthyl	403
4-chloro-2-cyclohexylphenoxy	2-(4-chlorophenylthio)pyridin-3-yl	550	4-chloro-3,5-dimethylphenoxy	550	2-methoxyphenyl	484
4-chloro-2-cyclohexylphenoxy	2,6-dimethylphenyl	435	4-chloro-3,5-dimethylphenoxy	435	3,4,5-trimethylphenyl	443
4-chloro-2-cyclohexylphenoxy	2,5-dimethoxyphenyl	467	4-chloro-3,5-dimethylphenoxy	467	3,4-dichlorophenyl	422

151

152

4-chloro-3,5-dimethylphenoxy	3-bromophenyl	432	4-chloro-3,5-dimethylphenoxy	3,5-dichlorophenyl	422
4-chloro-3,5-dimethylphenoxy	3-pyridyl	354	4-chloro-3,5-dimethylphenoxy	2-(propylthio)pyridin-3-yl	428
4-chloro-3,5-dimethylphenoxy	2-ethoxynaphth-1-yl	447	4-chloro-3,5-dimethylphenoxy	2-(ethylthio)pyridin-3-yl	414
4-chloro-3,5-dimethylphenoxy	2,3-dichlorophenyl	422	4-chloro-3,5-dimethylphenoxy	3-bromopyridin-5-yl	433
4-chloro-3,5-dimethylphenoxy	6-chloropyrid-3-yl	388	4-chloro-3,5-dimethylphenoxy	4-methyl-1,2,3-thiadiazol-5-yl	375
4-chloro-3,5-dimethylphenoxy	4-(trifluoromethoxy)phenyl	437	4-chloro-3,5-dimethylphenoxy	1-methyl-3-(2-(2-methyl)propyl)pyrazol-5-yl	413
4-chloro-3,5-dimethylphenoxy	2-fluoro-4-(trifluoromethyl)phenyl	439	4-chloro-3,5-dimethylphenoxy	3-chlorobenzo[b]thiophen-2-yl	443
4-chloro-3,5-dimethylphenoxy	3-bromothienyl	438	4-chloro-3,5-dimethylphenoxy	4-chlorophenyl	387
4-chloro-3,5-dimethylphenoxy	2-acetoxyphenyl	411	4-chloro-3,5-dimethylphenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	434
4-chloro-3,5-dimethylphenoxy	5-methylisoxazol-3-yl	358	4-chloro-3,5-dimethylphenoxy	benzo[b]thiophen-2-yl	409
4-chloro-3,5-dimethylphenoxy	2-(phenylthio)pyrid-3-yl	462	4-chloro-3,5-dimethylphenoxy	3,4-dimethylphenyl	381
4-chloro-3,5-dimethylphenoxy	2-(trifluoromethoxy)phenyl	437	4-chloro-3,5-dimethylphenoxy	2-(phenoxy)pyridin-3-yl	446
4-chloro-3,5-dimethylphenoxy	1-phenyl-5-propylpyrazin-4-yl	461	4-chloro-3,5-dimethylphenoxy	2-(methylthio)pyridin-3-yl	400
4-chloro-3,5-dimethylphenoxy	2-ethoxyphenyl	397	4-chloro-3,5-dimethylphenoxy	5-methyl-3-phenylisoxazol-4-yl	434
4-chloro-3,5-dimethylphenoxy	3-chlorothien-2-yl	393	4-chloro-3,5-dimethylphenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	456
4-chloro-3,5-dimethylphenoxy	1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl	413			

153

4-chloro-3,5-dimethylphenoxy	2-chloro-6-methylpyridin-4-yl	402	4-chloro-3,5-dimethylphenoxy	4-buty1phenyl	409
4-chloro-3,5-dimethylphenoxy	3,5-dimethylisoxazol-4-yl	372	4-chloro-3,5-dimethylphenoxy	2-methyl1phenyl	367
4-chloro-3,5-dimethylphenoxy	1-naphthyl	403	4-chloro-3,5-dimethylphenoxy	phenyl	353
4-chloro-3,5-dimethylphenoxy	2-fluorophenyl	371	4-chloro-3,5-dimethylphenoxy	4-ethylphenyl	381
4-chloro-3,5-dimethylphenoxy	4-propylphenyl	395	4-chloro-3,5-dimethylphenoxy	2,3-difluorophenyl	389
4-chloro-3,5-dimethylphenoxy	3-fluorophenyl	371	4-chloro-3,5-dimethylphenoxy	2,6-dimethoxyphenyl	413
4-chloro-3,5-dimethylphenoxy	2,6-difluorophenyl	389	4-chloro-3,5-dimethylphenoxy	3,4-difluorophenyl	389
4-chloro-3,5-dimethylphenoxy	2-chlorophenyl	387	4-chloro-3,5-dimethylphenoxy	2,5-difluorophenyl	389
4-chloro-3,5-dimethylphenoxy	3-(chloromethyl)phenyl	401	4-chloro-3,5-dimethylphenoxy	4-ethoxyphenyl	397
4-chloro-3,5-dimethylphenoxy	4-(2-(2-methyl)propyl)phenyl	409	4-chloro-3,5-dimethylphenoxy	2,4,6-trichlorophenyl	456
4-chloro-3,5-dimethylphenoxy	3-chlorophenyl	387	4-chloro-3,5-dimethylphenoxy	3-methyl1phenyl	367
4-chloro-3,5-dimethylphenoxy	3,5-dimethoxyphenyl	413	4-chloro-3,5-dimethylphenoxy	2-fluoro-5-(trifluoromethyl)phenyl	439
4-chloro-3,5-dimethylphenoxy	2,6-dichlorophenyl	422	4-chloro-3,5-dimethylphenoxy	3-methoxyphenyl	383
4-chloro-3,5-dimethylphenoxy	2,4-dichlorophenyl	422	4-chloro-3,5-dimethylphenoxy	2-bromophenyl	432
4-chloro-3,5-dimethylphenoxy	4-fluorophenyl	371	4-chloro-3,5-dimethylphenoxy	4-bromophenyl	432

154

155

156

4-chloro-3,5-dimethylphenoxy	4-fluoro-3-(trifluoromethyl)phenyl	439	4-chloro-3,5-dimethylphenoxy	2-chloro-6-methoxypyridin-4-yl	418
3-(trifluoromethoxy)phenyl		437	4-chloro-3,5-dimethylphenoxy	2,3-dichloropyridin-5-yl	423
4-chloro-3,5-dimethylphenoxy	9-fluoren-4-yl	455	4-chloro-3,5-dimethylphenoxy	1-naphthyl	417
4-chloro-3,5-dimethylphenoxy	isoxazol-5-yl	344	4-chloro-3,5-dimethylphenoxy	2,4-dimethoxyphenyl	413
benzofuran-5-yl		411	4-chloro-3,5-dimethylphenoxy	3-(4-bis(trifluoromethyl)phenyl	489
4-chloro-3,5-dimethylphenoxy	2-chloropyridin-3-yl	388	4-chloro-3,5-dimethylphenoxy	chlorophenoxy/pyridin-3-yl	480
4-chloro-3,5-dimethylphenoxy	2-(4-methylphenoxy)pyridin-3-yl	460	4-chloro-3,5-dimethylphenoxy	pentafluorophenyl	443
4-chloro-3,5-dimethylphenoxy	pyridin-4-yl	354	4-chloro-3,5-dimethylphenoxy	3,4-dimethoxyphenyl	351
4-chloro-3,5-dimethylphenoxy	anthraquinon-2-yl	483	pyrid-3-yloxy	2-(trifluoromethyl)phenyl	359
4-chloro-3,5-dimethylphenoxy	2-iodophenyl	479	pyrid-3-yloxy	2,4-difluorophenyl	327
4-chloro-3,5-dimethylphenoxy	4-pentylphenyl	423	pyrid-3-yloxy	3-(trifluoromethyl)phenyl	359
4-chloro-3,5-dimethylphenoxy	2-(4-chlorophenylthio)pyridin-3-yl	496	pyrid-3-yloxy	2-naphthyl	341
4-chloro-3,5-dimethylphenoxy	2,6-dimethylphenyl	381	pyrid-3-yloxy	2-methoxyphenyl	321
4-chloro-3,5-dimethylphenoxy	2,5-dimethoxyphenyl	413	pyrid-3-yloxy	3,4,5-trimethylphenyl	381
4-chloro-3,5-dimethylphenoxy	2,5-dichloropyridin-3-yl	423	pyrid-3-yloxy	3-bromophenyl	370
4-chloro-3,5-dimethylphenoxy	pyrid-3-yloxy		pyrid-3-yloxy	3-pyridyl	292
4-chloro-3,5-dimethylphenoxy	pyrid-3-yloxy		pyrid-3-yloxy	2-ethoxynaphth-1-yl	385
4-chloro-3,5-dimethylphenoxy	pyrid-3-yloxy		pyrid-3-yloxy	2,3-dichlorophenyl	360
4-chloro-3,5-dimethylphenoxy	pyrid-3-yloxy		pyrid-3-yloxy	6-chloropyrid-3-yl	327
4-chloro-3,5-dimethylphenoxy	pyrid-3-yloxy		pyrid-3-yloxy	4-(trifluoromethoxy)phenyl	375

157

pyrid-3-yloxy	2-fluoro-4-(trifluoromethyl)phenyl	377	pyrid-3-yloxy	2-(methylthio)pyridin-3-yl	338
pyrid-3-yloxy	3-bromothienyl	376	pyrid-3-yloxy	5-methyl-3-phenylisoxazol-4-yl	372
pyrid-3-yloxy	2-acetoxypyhenyl	349	pyrid-3-yloxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	395
pyrid-3-yloxy	5-methylisoxazol-3-yl	296	pyrid-3-yloxy	2-chloro-6-methylpyridin-4-yl	341
pyrid-3-yloxy	2-(phenylthio)pyrid-3-yl	400	pyrid-3-yloxy	3,5-dimethylisoxazol-4-yl	310
pyrid-3-yloxy	2-(trifluoromethoxy)phenyl	375	pyrid-3-yloxy	1-naphthyl	341
pyrid-3-yloxy	1-phenyl-5-propylpyrazin-4-yl	399	pyrid-3-yloxy	2-fluorophenyl	309
pyrid-3-yloxy	2-ethoxyphenyl	335	pyrid-3-yloxy	4-propylphenyl	333
pyrid-3-yloxy	3-chlorothien-2-yl	332	pyrid-3-yloxy	3-fluorophenyl	309
pyrid-3-yloxy	1-(2-(2-methyl)propyl)-3-methylpyrazol-5-yl	351	pyrid-3-yloxy	2,6-di fluorophenyl	327
pyrid-3-yloxy	3,5-dichlorophenyl	360	pyrid-3-yloxy	2-chlorophenyl	326
pyrid-3-yloxy	2-(propylthio)pyridin-3-yl	366	pyrid-3-yloxy	3-(chloromethyl)phenyl	340
pyrid-3-yloxy	2-(ethylthio)pyridin-3-yl	352	pyrid-3-yloxy	4-(2-(2-methyl)propyl)phenyl	347
pyrid-3-yloxy	3-bromopyridin-5-yl	371	pyrid-3-yloxy	3-chlorophenyl	326
pyrid-3-yloxy	4-methyl-1,2,3-thiadiazol-5-yl	313	pyrid-3-yloxy	3,5-dimethoxyphenyl	351
pyrid-3-yloxy	1-methyl-1-3-(2-(2-methyl)propyl)pyrazol-5-yl	351	pyrid-3-yloxy	2,6-dichlorophenyl	360
pyrid-3-yloxy	3-chlorobenzo[b]thiophen-2-yl	382	pyrid-3-yloxy	2,4-dichlorophenyl	360
pyrid-3-yloxy	4-chlorophenyl	326	pyrid-3-yloxy	4-fluorophenyl	309
pyrid-3-yloxy	4-methyl-1-2-phenyl-1,2,3-triazol-5-yl	372	pyrid-3-yloxy	4-butylphenyl	347
pyrid-3-yloxy	benzo[b]thiophen-2-yl	347	pyrid-3-yloxy	2-methylphenyl	305
pyrid-3-yloxy	3,4-dimethylphenyl	319	pyrid-3-yloxy	4-ethylphenyl	319
pyrid-3-yloxy	2-(phenoxy)pyridin-3-yl	384	pyrid-3-yloxy	2,3-difluorophenyl	327
			pyrid-3-yloxy	2,6-dimethoxyphenyl	351

158

pyrid-3-yloxy	2-(methylthio)pyridin-3-yl	338
pyrid-3-yloxy	5-methyl-3-phenylisoxazol-4-yl	372
pyrid-3-yloxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	395
pyrid-3-yloxy	2-chloro-6-methylpyridin-4-yl	341
pyrid-3-yloxy	3,5-dimethylisoxazol-4-yl	310
pyrid-3-yloxy	1-naphthyl	341
pyrid-3-yloxy	2-fluorophenyl	309
pyrid-3-yloxy	4-propylphenyl	333
pyrid-3-yloxy	3-fluorophenyl	309
pyrid-3-yloxy	2,6-di fluorophenyl	327
pyrid-3-yloxy	2-chlorophenyl	326
pyrid-3-yloxy	3-(chloromethyl)phenyl	340
pyrid-3-yloxy	4-(2-(2-methyl)propyl)phenyl	347
pyrid-3-yloxy	3-chlorophenyl	326
pyrid-3-yloxy	3,5-dimethoxyphenyl	351
pyrid-3-yloxy	2,6-dichlorophenyl	360
pyrid-3-yloxy	2,4-dichlorophenyl	360
pyrid-3-yloxy	4-fluorophenyl	309
pyrid-3-yloxy	4-butylphenyl	347
pyrid-3-yloxy	2-methylphenyl	305
pyrid-3-yloxy	4-ethylphenyl	319
pyrid-3-yloxy	2,3-difluorophenyl	327
pyrid-3-yloxy	2,6-dimethoxyphenyl	351

159

160

pyrid-3-yloxy	3,4-difluorophenyl	327	pyrid-3-yloxy	2-chloro-6-methoxypyridin-4-yl	357
pyrid-3-yloxy	2,5-difluorophenyl	327	pyrid-3-yloxy	2,3-dichloropyridin-5-yl	361
pyrid-3-yloxy	4-ethoxyphenyl	335	pyrid-3-yloxy	1-naphthyl	355
pyrid-3-yloxy	2,4,6-trichlorophenyl	395	pyrid-3-yloxy	2,4-dimethoxyphenyl	351
pyrid-3-yloxy	3-methylphenyl	305	pyrid-3-yloxy	3,5-bis(trifluoromethyl)phenyl	427
pyrid-3-yloxy	2-fluoro-5-(trifluoromethyl)phenyl	377	pyrid-3-yloxy	2-(4-chlorophenoxy)pyridin-3-yl	419
pyrid-3-yloxy	3-methoxyphenyl	321	pyrid-3-yloxy	2,4-difluorophenyl	381
pyrid-3-yloxy	2-bromophenyl	370	pyrid-3-yloxy	3,4-dimethoxyphenyl	429
pyrid-3-yloxy	4-bromophenyl	370	pyrid-3-yloxy	3-(trifluoromethyl)phenyl	437
pyrid-3-yloxy	4-fluoro-3-(trifluoromethoxy)phenyl	377	pyrid-3-yloxy	2,4-difluorophenyl	405
pyrid-3-yloxy	9-fluorenon-4-yl	375	4-bromophenoxy	3-(trifluoromethyl)phenyl	437
pyrid-3-yloxy	isoxazol-5-yl	393	4-bromophenoxy	2-naphthyl	419
pyrid-3-yloxy	benzofuroxan-5-yl	349	4-bromophenoxy	2-methoxyphenyl	399
pyrid-3-yloxy	2-chloropyrid-3-yl	327	4-bromophenoxy	3,4,5-trimethylphenyl	459
pyrid-3-yloxy	2-(4-methylphenoxy)pyridin-3-yl	398	4-bromophenoxy	3,4-dichlorophenyl	438
pyrid-3-yloxy	pyridin-4-yl	292	4-bromophenoxy	3-bromophenyl	448
pyrid-3-yloxy	anthraquinon-2-yl	421	4-bromophenoxy	3-pyridyl	370
pyrid-3-yloxy	2-iodophenyl	417	4-bromophenoxy	2-ethoxynaphth-1-yl	463
pyrid-3-yloxy	4-pentylophenyl	361	4-bromophenoxy	2,3-dichlorophenyl	438
pyrid-3-yloxy	2-(4-chlorophenylthio)pyridin-3-yl	435	4-bromophenoxy	6-chloropyrid-3-yl	405
pyrid-3-yloxy	pyridin-3-yl		4-bromophenoxy	4-(trifluoromethoxy)phenyl	453
pyrid-3-yloxy	2,6-dimethylphenyl	319	4-bromophenoxy	2-fluoro-4-(trifluoromethyl)phenyl	455
pyrid-3-yloxy	2,5-dimethoxyphenyl	354	4-bromophenoxy	3-bromothiaryl	454
pyrid-3-yloxy	2,5-dichloropyridin-3-yl	361	4-bromophenoxy	2-acetoxyphenyl	427

161

4-bromophenoxy	5-methylisoxazol-3-yl	374	4-bromophenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	473
4-bromophenoxy	2-(trifluoromethoxy)phenyl	478			
4-bromophenoxy	1-phenyl-5-propylpyrazin-4-yl	453			
4-bromophenoxy	2-ethoxyphenyl	477	4-bromophenoxy	2-chloro-6-methylpyridin-4-yl	419
4-bromophenoxy	3-chlorothien-2-yl	413	4-bromophenoxy	3,5-dimethylisoxazol-4-yl	388
4-bromophenoxy	1-(2-(2-methylpropyl)-3-methylpyrazol-5-yl	410	4-bromophenoxy	1-naphthyl	419
4-bromophenoxy	3,5-dichlorophenyl	429	4-bromophenoxy	2-fluorophenyl	387
4-bromophenoxy	2-(propylthio)pyridin-3-yl	438	4-bromophenoxy	4-propylphenyl	411
4-bromophenoxy	2-(ethylthio)pyridin-3-yl	444	4-bromophenoxy	3-fluorophenyl	387
4-bromophenoxy	3-bromopyridin-3-yl	450	4-bromophenoxy	2,6-difluorophenyl	405
4-bromophenoxy	4-methyl-1,2,3-thiadiazol-5-yl	449	4-bromophenoxy	2-chlorophenyl	414
4-bromophenoxy	4-methyl-1,2,3-thiadiazol-5-yl	391	4-bromophenoxy	3-(chloromethyl)phenyl	418
4-bromophenoxy	1-methyl-1-(2-(2-methylpropyl)pyrazol-5-yl	429	4-bromophenoxy	4-(2-(2-methylpropyl)phenyl)phenyl	425
4-bromophenoxy	3-chlorobenzo[b]thiophen-2-yl	460			
4-bromophenoxy	4-chlorophenyl	404	4-bromophenoxy	3-chlorophenyl	404
4-bromophenoxy	4-methyl-2-phenyl-1,2,3-triazol-5-yl	450	4-bromophenoxy	3,5-dimethoxyphenyl	429
4-bromophenoxy	benzo[b]thiophen-2-yl	425	4-bromophenoxy	2,6-dichlorophenyl	438
4-bromophenoxy	3,4-dimethylphenyl	397	4-bromophenoxy	2,4-dichlorophenyl	438
4-bromophenoxy	2-(phenoxy)pyridin-3-yl	462	4-bromophenoxy	4-fluorophenyl	387
4-bromophenoxy	2-(methylthio)pyridin-3-yl	416	4-bromophenoxy	4-butylphenyl	425
4-bromophenoxy	5-methyl-1-3-phenylisoxazol-4-yl	450	4-bromophenoxy	2-methylphenyl	383
4-bromophenoxy			4-bromophenoxy	phenyl	369
			4-bromophenoxy	4-ethylphenyl	397
			4-bromophenoxy	2,3-difluorophenyl	405
			4-bromophenoxy	4,6-dimethoxyphenyl	429
			4-bromophenoxy	3,4-difluorophenyl	405
			4-bromophenoxy	2,5-difluorophenyl	405

162

4-bromophenoxy	4-bromophenoxy	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	473
4-bromophenoxy	4-bromophenoxy	1-naphthyl	419
4-bromophenoxy	4-bromophenoxy	2-fluorophenyl	387
4-bromophenoxy	4-bromophenoxy	4-propylphenyl	411
4-bromophenoxy	4-bromophenoxy	3-fluorophenyl	387
4-bromophenoxy	4-bromophenoxy	2,6-difluorophenyl	405
4-bromophenoxy	4-bromophenoxy	2-chlorophenyl	414
4-bromophenoxy	4-bromophenoxy	3-(chloromethyl)phenyl	418
4-bromophenoxy	4-bromophenoxy	4-(2-(2-methylpropyl)phenyl)phenyl	425
4-bromophenoxy	4-bromophenoxy	3-chlorophenyl	404
4-bromophenoxy	4-bromophenoxy	2,6-dichlorophenyl	429
4-bromophenoxy	4-bromophenoxy	2,4-dichlorophenyl	438
4-bromophenoxy	4-bromophenoxy	4-fluorophenyl	387
4-bromophenoxy	4-bromophenoxy	4-butylphenyl	425
4-bromophenoxy	4-bromophenoxy	2-methylphenyl	383
4-bromophenoxy	4-bromophenoxy	phenyl	369
4-bromophenoxy	4-bromophenoxy	4-ethylphenyl	397
4-bromophenoxy	4-bromophenoxy	2,3-difluorophenyl	405
4-bromophenoxy	4-bromophenoxy	4,6-dimethoxyphenyl	429
4-bromophenoxy	4-bromophenoxy	3,4-difluorophenyl	405
4-bromophenoxy	4-bromophenoxy	2,5-difluorophenyl	405

163

164

164

4-bromophenoxy	413	4-bromophenoxy	2,3-dichloropyridin-5-yl	439
4-bromophenoxy	473	4-bromophenoxy	1-naphthyl	433
4-bromophenoxy	383	4-bromophenoxy	2,4-dimethoxyphenyl	429
4-bromophenoxy	455	4-bromophenoxy	3,5-bis(trifluoromethyl)phenyl	505
(trifluoromethyl)phenyl				
3-methoxyphenyl	399	4-bromophenoxy	2-(4-chlorophenoxy)pyridin-3-yl	497
2-bromophenyl	448	4-bromophenoxy	pentafluorophenyl	459
4-bromophenoxy	448	4-biphenyl		431
4-bromophenoxy	455	4-chloro-2-methylphenylthio	3,4-dimethoxyphenyl	415
(trifluoromethyl)phenyl		4-chloro-2-methylphenylthio		
3-(trifluoromethoxy)phenyl	453	4-chloro-2-methylphenylthio	2-(trifluoromethyl)phenyl	423
9-fluorenon-4-yl	471	4-chloro-2-methylphenylthio	2,4-difluorophenyl	391
isoxazol-5-yl	360	4-chloro-2-methylphenylthio	4-cyanophenyl	380
benzofuroxan-5-yl	427	4-chloro-2-methylphenylthio		
4-bromophenoxy		4-chloro-2-methylphenylthio		
2-chloropyrid-3-yl	360	4-chloro-2-methylphenylthio		
2-(4-methylphenoxy)pyridin-3-yl	476	4-chloro-2-methylphenylthio		
pyridin-4-yl	370	4-chloro-2-methylphenylthio	3-(trifluoromethyl)phenyl	423
4-bromophenoxy		4-chloro-2-methylphenylthio		
4-bromophenoxy	499	4-chloro-2-methylphenylthio		
4-bromophenoxy	495	4-chloro-2-methylphenylthio		
4-bromophenoxy	439	4-chloro-2-methylphenylthio		
4-bromophenoxy	513	4-chloro-2-methylphenylthio		
2-(4-chlorophenylthio)pyridin-3-yl		4-chloro-2-methylphenylthio		
2,6-dimethylphenyl	397	4-chloro-2-methylphenylthio	2-methoxyphenyl	385
2,5-dimethoxyphenyl	429	4-chloro-2-methylphenylthio		
4-bromophenoxy	439	4-chloro-2-methylphenylthio		
2-chloro-6-methoxypyridin-4-yl	435	4-chloro-2-methylphenylthio	4-nitrophenyl	400

165

4-chloro-2-methylphenylthio	3,4-dichlorophenyl	424	4-chloro-2-methylphenylthio	1-phenyl-5-propyl-pyrazin-4-yl	463
4-chloro-2-methylphenylthio	5-nitrofuran-2-yl	390	4-chloro-2-methylphenylthio	2-ethoxyphenyl	399
4-chloro-2-methylphenylthio	3-bromophenyl	434	4-chloro-2-methylphenylthio	3-chlorothien-2-yl	395
4-chloro-2-methylphenylthio	3-pyridyl	356	4-chloro-2-methylphenylthio	1-(2-(2-methylpropyl)-3-methylpyrazol-5-yl)	415
4-chloro-2-methylphenylthio	2-ethoxyxanthphth-1-yl	449	4-chloro-2-methylphenylthio	3,5-dichlorophenyl	424
4-chloro-2-methylphenylthio	2,3-dichlorophenyl	424	4-chloro-2-methylphenylthio	2-(propylthio)pyridin-3-yl	430
4-chloro-2-methylphenylthio	3-nitrophenyl	400	4-chloro-2-methylphenylthio	2-(ethylthio)pyridin-3-yl	416
4-chloro-2-methylphenylthio	6-chloropyrid-3-yl	390	4-chloro-2-methylphenylthio	3-bromopyridin-5-yl	435
4-chloro-2-methylphenylthio	4-(trifluoromethoxy)phenyl	439	4-chloro-2-methylphenylthio	4-methyl-1,2,3-thiadiazol-5-yl	377
4-chloro-2-methylphenylthio	2-fluoro-4-(trifluoromethyl)phenyl	441	4-chloro-2-methylphenylthio	1-methyl-1-3-(2-(2-methylpropyl)pyrazol-5-yl)	415
4-chloro-2-methylphenylthio	3-bromothienyl	440	4-chloro-2-methylphenylthio	3-chlorobenzo[b]thiophen-2-yl	445
4-chloro-2-methylphenylthio	2-acetoxyphenyl	413	4-chloro-2-methylphenylthio	4-chlorophenyl	389
4-chloro-2-methylphenylthio	5-methylisoxazol-3-yl	360	4-chloro-2-methylphenylthio	4-methyl-2-phenyl-1,2,3-triazol-5-yl	436
4-chloro-2-methylphenylthio	2-(phenylthio)pyrid-3-yl	464	4-chloro-2-methylphenylthio	benzo[b]thiophen-2-yl	411
4-chloro-2-methylphenylthio	2-(trifluoromethoxy)phenyl	439	4-chloro-2-methylphenylthio	3,4-dimethylphenyl	383

166

4-chloro-2-methylphenylthio	4-chloro-2-methylphenylthio	463	4-chloro-2-methylphenylthio	1-phenyl-5-propyl-pyrazin-4-yl	463
4-chloro-2-methylphenylthio	4-chloro-2-methylphenylthio	399	4-chloro-2-methylphenylthio	2-ethoxyphenyl	399
4-chloro-2-methylphenylthio	3-chlorothien-2-yl	395	4-chloro-2-methylphenylthio	3-chlorothien-2-yl	395
4-chloro-2-methylphenylthio	1-(2-(2-methylpropyl)-3-methylpyrazol-5-yl)	415	4-chloro-2-methylphenylthio	1-(2-(2-methylpropyl)pyrazol-5-yl)	415
4-chloro-2-methylphenylthio	3,5-dichlorophenyl	424	4-chloro-2-methylphenylthio	3,5-dichlorophenyl	424
4-chloro-2-methylphenylthio	2-(propylthio)pyridin-3-yl	430	4-chloro-2-methylphenylthio	2-(propylthio)pyridin-3-yl	430
4-chloro-2-methylphenylthio	2-(ethylthio)pyridin-3-yl	416	4-chloro-2-methylphenylthio	2-(ethylthio)pyridin-3-yl	416
4-chloro-2-methylphenylthio	3-bromopyridin-5-yl	435	4-chloro-2-methylphenylthio	3-bromopyridin-5-yl	435
4-chloro-2-methylphenylthio	4-methyl-1,2,3-thiadiazol-5-yl	377	4-chloro-2-methylphenylthio	4-methyl-1,2,3-thiadiazol-5-yl	377
4-chloro-2-methylphenylthio	1-methyl-1-3-(2-(2-methylpropyl)pyrazol-5-yl)	415	4-chloro-2-methylphenylthio	1-methyl-1-3-(2-(2-methylpropyl)pyrazol-5-yl)	415
4-chloro-2-methylphenylthio	benzo[b]thiophen-2-yl	445	4-chloro-2-methylphenylthio	benzo[b]thiophen-2-yl	445
4-chloro-2-methylphenylthio	3,4-dimethylphenyl	383	4-chloro-2-methylphenylthio	3,4-dimethylphenyl	383

167

168

4-chloro-2-methylphenylthio	2-(phenoxy)pyridin-3-yl	448	4-chloro-2-methylphenylthio	3-chlorophenyl	389
4-chloro-2-methylphenylthio	2-(methylthio)pyridin-3-yl	402	4-chloro-2-methylphenylthio	2-nitrophenyl	400
4-chloro-2-methylphenylthio	5-methyl-3-phenylisoxazol-4-yl	436	4-chloro-2-methylphenylthio	3,5-dimethoxyphenyl	415
4-chloro-2-methylphenylthio	4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridin-3-yl	458	4-chloro-2-methylphenylthio	2,6-dichlorophenyl	424
4-chloro-2-methylphenylthio	2-chloro-6-methylpyridin-4-yl	404	4-chloro-2-methylphenylthio	2,4-dichlorophenyl	424
4-chloro-2-methylphenylthio	3,5-dimethylisoxazol-4-yl	374	4-chloro-2-methylphenylthio	4-fluorophenyl	373
4-chloro-2-methylphenylthio	1-naphthyl	405	4-chloro-2-methylphenylthio	4-butylphenyl	411
4-chloro-2-methylphenylthio	2-fluorophenyl	373	4-chloro-2-methylphenylthio	2-methylphenyl	369
4-chloro-2-methylphenylthio	4-propylphenyl	397	4-chloro-2-methylphenylthio	phenyl	355
4-chloro-2-methylphenylthio	4-(trifluoromethyl)phenyl	423	4-chloro-2-methylphenylthio	4-ethylphenyl	383
4-chloro-2-methylphenylthio	3-fluorophenyl	373	4-chloro-2-methylphenylthio	2,3-difluorophenyl	391
4-chloro-2-methylphenylthio	2,6-difluorophenyl	391	4-chloro-2-methylphenylthio	2,6-dimethoxyphenyl	415
4-chloro-2-methylphenylthio	2-chlorophenyl	389	4-chloro-2-methylphenylthio	3,4-difluorophenyl	391
4-chloro-2-methylphenylthio	4-(2-(2-methylpropyl)phenyl	411	4-chloro-2-methylphenylthio	2,5-difluorophenyl	391

169	3-methylphenyl	369	4-chloro-2-methylphenylthio	481
441	2-fluoro-5-(trifluoromethyl)phenyl	441	4-chloro-2-methylanilino	414
385	3-methoxyphenyl	385	4-chloro-2-methylanilino	398
361	thien-2-yl	361	4-chloro-2-methylanilino	406
434	2-bromophenyl	434	4-chloro-2-methylanilino	374
434	4-bromophenyl	434	4-chloro-2-methylanilino	363
441	4-fluoro-3-(trifluoromethyl)phenyl	441	4-chloro-2-methylanilino	406
439	3-(trifluoromethoxy)phenyl	439	4-chloro-2-methylanilino	363
457	9-fluoren-4-yl	457	4-chloro-2-methylanilino	388
346	isoxazol-5-yl	346	4-chloro-2-methylanilino	368
413	benzofuran-5-yl	413	4-chloro-2-methylanilino	428
390	2-chloropyrid-3-yl	390	4-chloro-2-methylanilino	383
391	3,5-difluorophenyl	391	4-chloro-2-methylanilino	407
462	2-(4-methylphenoxy)pyridin-3-yl	462	4-chloro-2-methylanilino	373
356	pyridin-4-yl	356	4-chloro-2-methylanilino	417
485	anthraquinon-2-yl	485	4-chloro-2-methylanilino	339
			4-chloro-2-methylanilino	

4-chloro-2-methylanilino	2-ethoxynaphth-1-yl	432	4-chloro-2-methylanilino	2-(propylthio)pyridin-3-yl	413
4-chloro-2-methylanilino	2,3-dichlorophenyl	407	4-chloro-2-methylanilino	2-(ethylthio)pyridin-3-yl	399
4-chloro-2-methylanilino	3-nitrophenyl	383	4-chloro-2-methylanilino	3-bromopyridin-5-yl	418
4-chloro-2-methylanilino	6-chloropyrid-3-yl	373	4-chloro-2-methylanilino	4-methyl-1,2,3-thiadiazol-5-yl	360
4-chloro-2-methylanilino	4-(trifluoromethoxy)phenyl	422	4-chloro-2-methylanilino	1-methyl-1,3-(2,2-methyl)propyl)pyrazol-5-yl	398
4-chloro-2-methylanilino	2-fluoro-4-(trifluoromethyl)phenyl	424	4-chloro-2-methylanilino	3-chlorobenzo[b]thiophen-2-yl	428
4-chloro-2-methylanilino	3-bromothienyl	423	4-chloro-2-methylanilino	4-chlorophenyl	372
4-chloro-2-methylanilino	2-acetoxypyphenyl	396	4-chloro-2-methylanilino	4-methyl-2-phenyl-1,2,3-triazol-5-yl	419
4-chloro-2-methylanilino	5-methylisoxazol-3-yl	343	4-chloro-2-methylanilino	benzo[b]thiophen-2-yl	394
4-chloro-2-methylanilino	2-(phenylthio)pyrid-3-yl	447	4-chloro-2-methylanilino	3,4-dimethylphenyl	366
4-chloro-2-methylanilino	2-(trifluoromethoxy)phenyl	422	4-chloro-2-methylanilino	2-(phenoxy)pyridin-3-yl	431
4-chloro-2-methylanilino	1-phenyl-5-propylpyrazin-4-yl	446	4-chloro-2-methylanilino	2-(methylthio)pyridin-3-yl	385
4-chloro-2-methylanilino	2-ethoxyphenyl	382	4-chloro-2-methylanilino	5-methyl-1,3-phenylisoxazol-4-yl	419
4-chloro-2-methylanilino	3-chlorothien-2-yl	378	4-chloro-2-methylanilino	4-chloro-1,3-dimethylpyrazol[3,4-b]pyridin-3-yl	441
4-chloro-2-methylanilino	1-(2-(2-methylpropyl)-3-methylpyrazol-5-yl	398	4-chloro-2-methylanilino	2-chloro-6-methylpyridin-4-yl	387
4-chloro-2-methylanilino	3,5-dichlorophenyl	407	4-chloro-2-methylanilino	2-chloro-6-methylpyridin-4-yl	387

173

113

4-chloro-2-methylanilino	3,5-dimethylisoxazol-4-yl	357
4-chloro-2-methylanilino	1-naphthyl	388
4-chloro-2-methylanilino	2-fluorophenyl	356
4-chloro-2-methylanilino	4-propylphenyl	380
4-chloro-2-methylanilino	4-(trifluoromethyl)phenyl	406
4-chloro-2-methylanilino	3-fluorophenyl	356
4-chloro-2-methylanilino	2,6-difluorophenyl	374
4-chloro-2-methylanilino	2-chlorophenyl	372
4-chloro-2-methylanilino	3-(chloromethyl)phenyl	386
4-chloro-2-methylanilino	4-(2-(2-methyl)propyl)phenyl	394
4-chloro-2-methylanilino	3-chlorophenyl	372
4-chloro-2-methylanilino	2-nitrophenyl	383
4-chloro-2-methylanilino	3,5-dimethoxyphenyl	398
4-chloro-2-methylanilino	2,6-dichlorophenyl	407
4-chloro-2-methylanilino	2,4-dichlorophenyl	407

175

176

4-chloro-2-methylanilino

2-bromophenyl

417

4-chloro-2-methylanilino

4-bromophenyl

417

4-chloro-2-methylanilino

4-fluoro-3-(trifluoromethoxy)phenyl

424

4-chloro-2-methylanilino

9-fluoren-4-yl

440

4-chloro-2-methylanilino

isoxazol-5-yl

329

4-chloro-2-methylanilino

benzofuran-5-yl

396

4-chloro-2-methylanilino

2-chloropyrid-3-yl

373

4-chloro-2-methylanilino

3,5-difluorophenyl

374

4-chloro-2-methylanilino

2-(4-methylphenoxy)pyridin-3-yl

445

4-chloro-2-methylanilino

pyridin-4-yl

339

4-chloro-2-methylanilino

anthraquinon-2-yl

468

4-chloro-2-methylanilino

2-iodophenyl

464

The compounds listed in Table 7 can be prepared from substituted 5-aminopyridine compounds and the appropriate acid chloride according to the general procedure above.

Table 7

R^XR^J

4-chloro-2-methoxyphenoxyl 3,4-difluorophenyl

4-chloro-2-methoxyphenoxyl 4-pentylphenyl

4-chloro-2-methoxyphenoxyl 2-(4-chlorophenylthio)pyridin-3-yl

4-chloro-2-methoxyphenoxyl 2,6-dimethylphenyl

4-chloro-2-methoxyphenoxyl 2,5-dimethoxyphenyl

4-chloro-2-methoxyphenoxyl 2,5-dichloropyridin-3-yl

4-chloro-2-methoxyphenoxyl 2-chloro-6-methoxypyridin-4-yl

4-chloro-2-methoxyphenoxyl 2,3-dichloropyridin-5-yl

4-chloro-2-methoxyphenoxyl 1-naphthyl

4-chloro-2-methoxyphenoxyl 2,4-dimethoxyphenyl

4-chloro-2-methoxyphenoxyl 3,5-bis(trifluoromethyl)phenyl

4-chloro-2-methoxyphenoxyl 2-(4-chlorophenoxy)pyridin-3-yl

4-chloro-2-methoxyphenoxyl pentafluorophenyl

4-chloro-2-methoxyphenoxyl 4-pentylphenyl

4-chloro-2-methoxyphenoxyl 2-(4-chlorophenylthio)pyridin-3-yl

4-chloro-2-methoxyphenoxyl 2,6-dimethylphenyl

4-chloro-2-methoxyphenoxyl 2,5-dimethoxyphenyl

4-chloro-2-methoxyphenoxyl 2,5-dichloropyridin-3-yl

4-chloro-2-methoxyphenoxyl 2-chloro-6-methoxypyridin-4-yl

4-chloro-2-methoxyphenoxyl 2,3-dichloropyridin-5-yl

4-chloro-2-methoxyphenoxyl 1-naphthyl

4-chloro-2-methoxyphenoxyl 2,4-dimethoxyphenyl

4-chloro-2-methoxyphenoxyl 3,5-bis(trifluoromethyl)phenyl

4-chloro-2-methoxyphenoxyl 2-(4-chlorophenoxy)pyridin-3-yl

4-chloro-2-methoxyphenoxyl pentafluorophenyl

4-chloro-2-methoxyphenoxyl 4-pentylphenyl

4-chloro-2-methoxyphenoxyl 2-(4-chlorophenylthio)pyridin-3-yl

4-chloro-2-methoxyphenoxyl 2,6-dimethylphenyl

4-chloro-2-methoxyphenoxyl 2,5-dimethoxyphenyl

4-chloro-2-methoxyphenoxyl 2,5-dichloropyridin-3-yl

4-chloro-2-methoxyphenoxyl 2-chloro-6-methoxypyridin-4-yl

4-chloro-2-methoxyphenoxyl 2,3-dichloropyridin-5-yl

4-chloro-2-methoxyphenoxyl 1-naphthyl

4-chloro-2-methoxyphenoxyl 2,4-dimethoxyphenyl

4-chloro-2-methoxyphenoxyl 3,5-bis(trifluoromethyl)phenyl

4-chloro-2-methoxyphenoxyl 2-(4-chlorophenoxy)pyridin-3-yl

4-chloro-2-methoxyphenoxyl pentafluorophenyl

4-chloro-2-methoxyphenoxyl 4-pentylphenyl

4-chloro-2-methoxyphenoxyl 2-(4-chlorophenylthio)pyridin-3-yl

4-chloro-2-methoxyphenoxyl 2,6-dimethylphenyl

4-chloro-2-methoxyphenoxyl 2,5-dimethoxyphenyl

4-chloro-2-methoxyphenoxyl 2,5-dichloropyridin-3-yl

4-chloro-2-methoxyphenoxyl 2-chloro-6-methoxypyridin-4-yl

4-chloro-2-methoxyphenoxyl 2,3-dichloropyridin-5-yl

The compounds listed in Table 7 can be prepared from substituted 5-aminopyridine compounds and the appropriate acid chloride according to the general procedure above.

177

3-fluoro-5-methylphenoxy	2,3-dichloropyridin-5-yl
3-fluoro-5-methylphenoxy	1-naphthyl
3-fluoro-5-methylphenoxy	2,4-dimethoxyphenyl
3-fluoro-5-methylphenoxy	3,5-bis(trifluoromethyl)phenyl
3-fluoro-5-methylphenoxy	2-(4-chlorophenoxy)pyridin-3-yl
3-fluoro-5-methylphenoxy	pentafluorophenyl
3-fluoro-5-methylphenoxy	4-pentyloxy
2-methylpyrid-3-yloxy	2-(4-chlorophenylthio)pyridin-3-yl
2-methylpyrid-3-yloxy	2,6-dimethylphenyl
2-methylpyrid-3-yloxy	2,5-dimethoxyphenyl
2-methylpyrid-3-yloxy	2,5-dichloropyridin-3-yl
2-methylpyrid-3-yloxy	2-chloro-6-methoxypyridin-4-yl
2-methylpyrid-3-yloxy	2,3-dichloropyridin-5-yl
2-methylpyrid-3-yloxy	1-naphthyl
2-methylpyrid-3-yloxy	2,4-dimethoxyphenyl
2-methylpyrid-3-yloxy	3,5-bis(trifluoromethyl)phenyl
2-methylpyrid-3-yloxy	2-(4-chlorophenoxy)pyridin-3-yl
2-methylpyrid-3-yloxy	pentafluorophenyl
4-methoxyphenoxy	4-biphenyl
4-methoxyphenoxy	4-cyanophenyl
4-methoxyphenoxy	3-cyanophenyl
4-methoxyphenoxy	4-nitrophenyl
4-methoxyphenoxy	5-nitrofuran-2-yl

180

179

4-methoxyphenoxy	3-nitrophenyl
4-(trifluoromethyl)phenoxy	4-chlorophenoxy
4-methoxyphenoxy	2-nitrophenyl
4-methoxyphenoxy	thien-2-yl
2-(2-propoxy)phenoxy	4-biphenyl
2-(2-propoxy)phenoxy	4-cyanophenyl
2-(2-propoxy)phenoxy	3-cyanophenyl
2-(2-propoxy)phenoxy	4-nitrophenyl
2-(2-propoxy)phenoxy	5-nitrofuran-2-yl
2-(2-propoxy)phenoxy	thien-2-yl
2-(2-propoxy)phenoxy	3,5-difluorophenyl
2-(2-propoxy)phenoxy	2,4-difluorophenoxy
2-(2-propoxy)phenoxy	4-biphenyl
4-fluorophenoxy	4-cyanophenyl
4-fluorophenoxy	3-cyanophenyl
4-fluorophenoxy	4-nitrophenyl
4-fluorophenoxy	5-nitrofuran-2-yl
4-fluorophenoxy	3-nitrophenyl
4-fluorophenoxy	2-nitrophenyl
4-fluorophenoxy	4-(trifluoromethyl)phenyl
4-fluorophenoxy	thien-2-yl
4-fluorophenoxy	3,5-difluorophenyl
4-chlorophenoxy	4-biphenyl
4-chlorophenoxy	4-cyanophenyl
4-chlorophenoxy	3-cyanophenyl
4-chlorophenoxy	4-nitrophenyl
4-chlorophenoxy	5-nitrofuran-2-yl
4-chlorophenoxy	2,4-difluorophenoxy
4-chlorophenoxy	4-biphenyl
4-chlorophenoxy	4-cyanophenyl
4-chlorophenoxy	3-cyanophenyl
4-chlorophenoxy	4-nitrophenyl
4-chlorophenoxy	5-nitrofuran-2-yl
4-chlorophenoxy	2,4-difluorophenoxy
4-chlorophenoxy	4-biphenyl
4-chlorophenoxy	4-cyanophenyl
4-chlorophenoxy	3-cyanophenyl
4-chlorophenoxy	4-nitrophenyl
4-chlorophenoxy	5-nitrofuran-2-yl

181

4-chloro-2, 5-dimethylphenoxy	thien-2-yl	4-(2-(2-methyl)propyl) phenoxy	3-nitrophenyl
4-chloro-2, 5-dimethylphenoxy	3, 5-difluorophenyl	4-(2-(2-methyl)propyl) phenoxy	4-(trifluoromethyl)phenyl
4-methoxyphenoxy	3, 5-difluorophenyl	4-(2-(2-methyl)propyl) phenoxy	2-nitrophenyl
2-(2-propoxy)phenoxy	4-(trifluoromethyl)phenyl	4-(2-(2-methyl)propyl) phenoxy	thien-2-yl
2, 4-difluorophenoxy	thien-2-yl	4-(2-(2-methyl)propyl) phenoxy	thien-2-yl
2, 4-difluorophenoxy	3, 5-difluorophenyl	4-(2-(2-methyl)propyl) phenoxy	3, 5-difluorophenyl
4-thiomethylphenoxy	4-biphenyl	4-(2-(2-methyl)propyl) phenoxy	4-biphenyl
4-thiomethylphenoxy	4-cyanophenyl	2, 3-dimethylphenoxy	2, 3-dimethylphenoxy
4-thiomethylphenoxy	3-cyanophenyl	2, 3-dimethylphenoxy	4-cyanophenyl
4-thiomethylphenoxy	4-nitrophenyl	2, 3-dimethylphenoxy	3-cyanophenyl
4-thiomethylphenoxy	5-nitrofuran-2-yl	2, 3-dimethylphenoxy	4-nitrophenyl
4-thiomethylphenoxy	3-nitrophenyl	2, 3-dimethylphenoxy	5-nitrofuran-2-yl
4-thiomethylphenoxy	4-(trifluoromethyl)phenyl	2, 3-dimethylphenoxy	3-nitrophenyl
4-thiomethylphenoxy	2-nitrophenyl	4-(trifluoromethyl)phenyl	4-(trifluoromethyl)phenyl
4-thiomethylphenoxy	thien-2-yl	2, 3-dimethylphenoxy	thien-2-yl
4-thiomethylphenoxy	3, 5-difluorophenyl	2, 3-dimethylphenoxy	3, 5-difluorophenyl
4-(2-(2-methyl)propyl)phenoxy	4-biphenyl	3, 5-(bis-2-propyl)phenoxy	4-biphenyl
4-(2-(2-methyl)propyl)phenoxy	4-cyanophenyl	3, 5-(bis-2-propyl)phenoxy	4-cyanophenyl
4-(2-(2-methyl)propyl)phenoxy	3-cyanophenyl	3, 5-(bis-2-propyl)phenoxy	3-cyanophenyl
4-(2-(2-methyl)propyl)phenoxy	4-nitrophenyl	3, 5-(bis-2-propyl)phenoxy	4-nitrophenyl
4-(2-(2-methyl)propyl)phenoxy	5-nitrofuran-2-yl	3, 5-(bis-2-propyl)phenoxy	5-nitrofuran-2-yl
4-(2-(2-methyl)propyl)phenoxy	5-nitrofuran-2-yl	3, 5-(bis-2-propyl)phenoxy	3-nitrophenyl

3,5-(bis-2-propyl)phenoxy	thien-2-yl	2,4-dichlorophenoxy	2-nitrophenyl
3-trifluoromethyl phenoxy	4-biphenyl	2,4-dichlorophenoxy	thien-2-yl
3-trifluoromethyl phenoxy	3,5-difluorophenyl	2,4-dichlorophenoxy	3,5-difluorophenyl
3-trifluoromethyl phenoxy	3-cyanophenyl	4-chloro-3-methylphenoxy	4-biphenyl
3-trifluoromethyl phenoxy	4-nitrophenyl	4-chloro-3-methylphenoxy	4-cyanophenyl
3-trifluoromethyl phenoxy	5-nitrofuran-2-yl	4-chloro-3-methylphenoxy	3-cyanophenyl
3-trifluoromethyl phenoxy	3-nitrophenyl	4-chloro-3-methylphenoxy	4-nitrophenyl
3-trifluoromethyl phenoxy	4-(trifluoromethyl)phenyl	4-chloro-3-methylphenoxy	5-nitrofuran-2-yl
3-trifluoromethyl phenoxy	thien-2-yl	4-chloro-3-methylphenoxy	3-nitrophenyl
3-trifluoromethyl phenoxy	3,5-difluorophenyl	4-chloro-3-methylphenoxy	2-nitrophenyl
2,6-dichlorophenoxy	4-biphenyl	4-chloro-3-methylphenoxy	thien-2-yl
2,6-dichlorophenoxy	4-cyanophenyl	4-chloro-3-methylphenoxy	3,5-difluorophenyl
2,6-dichlorophenoxy	3-cyanophenyl	4-chloro-3-methylphenoxy	4-biphenyl
2,6-dichlorophenoxy	5-nitrofuran-2-yl	4-chloro-3-methylphenoxy	4-cyanophenyl
2,6-dichlorophenoxy	3-nitrophenyl	4-chloro-3-methylphenoxy	5-nitrofuran-2-yl
2,6-dichlorophenoxy	4-(trifluoromethyl)phenyl	4-chloro-3-methylphenoxy	3-nitrophenyl
2,6-dichlorophenoxy	thien-2-yl	4-chloro-3-methylphenoxy	4-biphenyl
2,6-dichlorophenoxy	2-nitrophenyl	4-chloro-2-	4-cyanophenyl
2,6-dichlorophenoxy	3-nitrophenyl	cyclohexylphenoxy	3-cyanophenyl
2,6-dichlorophenoxy	4-(trifluoromethyl)phenyl	4-chloro-2-	cyclohexylphenoxy
2,6-dichlorophenoxy	thien-2-yl	cyclohexylphenoxy	4-biphenyl
2,6-dichlorophenoxy	3,5-difluorophenyl	4-chloro-2-	4-cyanophenyl
2,6-dichlorophenoxy	4-biphenyl	cyclohexylphenoxy	5-nitrofuran-2-yl
2,4-dichlorophenoxy	4-cyanophenyl	4-chloro-2-	3-nitrophenyl
2,4-dichlorophenoxy	3-cyanophenyl	cyclohexylphenoxy	4-(trifluoromethyl)phenyl
2,4-dichlorophenoxy	4-nitrophenyl	4-chloro-2-	4-cyanophenyl
2,4-dichlorophenoxy	5-nitrofuran-2-yl	cyclohexylphenoxy	3-nitrophenyl
2,4-dichlorophenoxy	3-nitrophenyl	4-chloro-2-	2-nitrophenyl

185

4-chloro-2-cyclohexylphenoxy	thien-2-yl
4-chloro-2-cyclohexylphenoxy	3,5-difluorophenyl
4-chloro-3,5-dimethylphenoxy	4-biphenyl
4-chloro-3,5-dimethylphenoxy	4-cyanophenyl
4-chloro-3,5-dimethylphenoxy	3-cyanophenyl
4-chloro-3,5-dimethylphenoxy	4-nitrophenoxy
4-chloro-3,5-dimethylphenoxy	5-nitrofuran-2-yl
4-chloro-3,5-dimethylphenoxy	3-nitrophenoxy
4-chloro-3,5-dimethylphenoxy	4-(trifluoromethyl)phenyl
4-chloro-3,5-dimethylphenoxy	2-nitrophenoxy
4-chloro-3,5-dimethylphenoxy	thien-2-yl
4-chloro-3,5-dimethylphenoxy	3,5-difluorophenyl
4-chloro-3,5-dimethylphenoxy	4-biphenyl
4-chloro-3,5-dimethylphenoxy	4-cyanophenyl
4-chloro-3,5-dimethylphenoxy	3-cyanophenyl
4-chloro-3,5-dimethylphenoxy	4-nitrophenoxy
4-chloro-3,5-dimethylphenoxy	5-nitrofuran-2-yl
4-chloro-3,5-dimethylphenoxy	3-nitrophenoxy
4-chloro-3,5-dimethylphenoxy	4-(trifluoromethyl)phenyl
4-chloro-3,5-dimethylphenoxy	2-nitrophenoxy
4-chloro-3,5-dimethylphenoxy	thien-2-yl
4-chloro-3,5-dimethylphenoxy	3,5-difluorophenyl
4-chloro-3,5-dimethylphenoxy	4-biphenyl
4-chloro-3,5-dimethylphenoxy	4-cyanophenyl
4-chloro-3,5-dimethylphenoxy	3-cyanophenyl
4-chloro-3,5-dimethylphenoxy	4-nitrophenoxy
4-chloro-3,5-dimethylphenoxy	5-nitrofuran-2-yl
4-chloro-3,5-dimethylphenoxy	3-nitrophenoxy

pyrid-3-yloxy	4-(trifluoromethyl)phenyl
pyrid-3-yloxy	2-nitrophenyl
pyrid-3-yloxy	thien-2-yl
pyrid-3-yloxy	3,5-difluorophenyl
4-bromophenoxy	4-biphenyl
4-bromophenoxy	4-Cyanophenyl
4-bromophenoxy	3-Cyanophenyl
4-bromophenoxy	4-nitrophenyl
4-bromophenoxy	5-nitrofuran-2-yl
4-bromophenoxy	3-nitrophenyl
4-bromophenoxy	4-(trifluoromethyl)phenyl
4-bromophenoxy	thien-2-yl
4-bromophenoxy	3,5-difluorophenyl
4-bromophenoxy	4-pentylphenyl
4-bromophenoxy	2-nitrophenyl
4-bromophenoxy	4-chloro-2-methylphenylthio
4-bromophenoxy	4-chloro-2-methylphenylthio
4-bromophenoxy	2,6-dimethylphenyl
4-chloro-2-methylphenylthio	2,5-dimethoxyphenyl
4-chloro-2-methylphenylthio	2,5-dichloropyridin-3-yl
4-chloro-2-methylphenylthio	2-chloro-6-methoxypyridin-4-yl
4-chloro-2-methylphenylthio	2,3-dichloropyridin-5-yl
4-chloro-2-methylphenylthio	1-naphthyl
4-chloro-2-	

187

188

188

4-chloro-2-methylphenylthio
2,4-dimethoxyphenyl

4-chloro-2-methylphenylthio
3,5-bis(trifluoromethyl)phenyl

4-chloro-2-methylphenylthio
2-(4-chlorophenoxy)pyridin-3-yl

4-chloro-2-methylphenylthio
pentafluorophenyl

4-chloro-2-methylphenylthio
4-pentylphenyl

4-chloro-2-methylanilino
2-(4-chlorophenylthio)pyridin-3-yl

4-chloro-2-methylanilino
2,6-dimethylphenyl

4-chloro-2-methylanilino
2,5-dichloropyridin-3-yl

4-chloro-2-methylanilino
2-chloro-6-methoxypyridin-4-yl

4-chloro-2-methylanilino
2,3-dichloropyridin-5-yl

4-chloro-2-methylanilino
1-naphthyl

4-chloro-2-methylanilino
2,4-dimethoxyphenyl

4-chloro-2-methylanilino
3,5-bis(trifluoromethyl)phenyl

4-chloro-2-methylanilino
2-(4-chlorophenoxy)pyridin-3-yl

4-chloro-2-methylanilino
pentafluorophenyl

Step A. General procedure for the preparation of 6-chloro-N-substituted nicotinamide.
To a suspension of 6-chloronicotinoyl chloride (11.76 g. (5.0 mmol)) in dry dichloromethane (10 mL) was added the amine (R^1R^2NH) (10.0 mmol) followed by the dropwise addition of triethylamine (1.7 mL, 12.2 mmol). After stirring for 40 min. at room temperature, the mixture was diluted with dichloromethane, washed with aqueous 1 M hydrochloric acid, saturated aqueous sodium hydrogencarbonate and water, dried over sodium sulfate and concentrated to dryness under reduced pressure to afford the desired nicotinamide.

The following compounds were prepared according to this procedure using the appropriate substituted amine:

6-Chloro-N-*o*-tolylnicotinamide: MS (*m/z*): 247/249 ($M+H$); $C_9H_9Cl_1F_1N_2O$ requires 246.5.

6-Chloro-N-(2-fluorophenyl)nicotinamide: MS (*m/z*): 251/253 ($M+H$); $C_9H_9Cl_1F_1N_2O$ requires 250.7.

6-Chloro-N-(2,6-dimethylphenyl)nicotinamide: MS (*m/z*): 261/263 ($M+H$); $C_{10}H_{11}Cl_1N_2O$ requires 260.7.

6-Chloro-N-(2-phenoxyphenyl)nicotinamide: MS (*m/z*): 325/327 ($M+H$); $C_{11}H_{11}Cl_1F_1N_2O$ requires 324.8.

6-Chloro-N-phenylnicotinamide: MS (*m/z*): 233/235 ($M+H$); $C_8H_7Cl_1N_2O$, requires 232.7.

6-Chloro-N-(2,4-difluorophenyl)nicotinamide: MS (*m/z*): 269/271 ($M+H$); $C_9H_8Cl_1F_2N_2O$ requires 268.6.

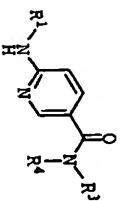
6-Chloro-N-(2,6-diisopropylphenyl)nicotinamide: MS (*m/z*): 317/319 ($M+H$); $C_{12}H_{15}Cl_1N_2O$ requires 316.8.

6-Chloro-N-(4-chlorophenyl)-N-methylnicotinamide: MS (*m/z*): 281/283 ($M+H$); $C_{10}H_{10}Cl_2N_2O$, requires 281.1.

6-Chloro-N-(4-chlorophenyl)nicotinamide: MS (*m/z*): 293/295 ($M+H$); $C_{10}H_9Cl_1N_2O$, requires 292.7.

6-Chloro-N-(3-methoxyphenyl)nicotinamide: MS (*m/z*): 326/328 ($M+H$); $C_{10}H_{10}Cl_1N_2O$, requires 327.7.

6-Chloro-N-(4-methoxyphenyl)nicotinamide: MS (*m/z*): 263/265 ($M+H$); $C_{10}H_{10}Cl_1N_2O$, requires 262.7.



Example 19

General procedure for the synthesis of 6-(substituted-5-amino)-N-substituted nicotinamides

189

6-Chloro-N-(2-methoxyphenyl)nicotinamide: MS (*m/z*): 263/265 (M+H)⁺; C₁₁H₁₁Cl₁N₂O, requires 262.7. 6-Chloro-N-methyl-N-phenylnicotinamide: MS (*m/z*): 247/249 (M+H)⁺; C₁₁H₁₁Cl₁N₂O, requires 246.7. 5-N-Benzyl-6-chloronicotinamide: MS (*m/z*): 247/249 (M+H)⁺; C₁₂H₁₃Cl₁N₂O, requires 246.7.

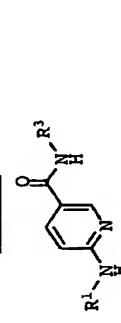
Step B. General procedure for the preparation of 6-Substituted-amino-N-substituted nicotinamides

10 A mixture of the 6-chloro-N-substituted nicotinamide (12.5 mmol) and amine (RNH₂ or R'NHCH₃) (20 mmol) in ethylene glycol (50 mL) or pyridine (alkylamines) (50 mL) was heated to 140°C for 20 hours. After cooling to room temperature, the mixture was diluted with dichloromethane/methanol (9:1, 250 mL) and filtered through a plug of silica gel, washing with additional dichloromethane/methanol (9:1, 250 mL). Concentration under reduced pressure afforded the desired 6-(substituted-amino)-N-substituted nicotinamide.

15 The compounds listed in Tables 8-11 were prepared from 6-chloro-N-substituted nicotinamides compounds and the appropriate amine according to the general procedure above.

25

Table 8

R¹

MS

*m/z*R¹

MS

*m/z*R¹

MS

*m/z*R¹

MS

*m/z*R¹

MS

*m/z*R¹

MS

m/z

189

6-Chloro-N-(2-methoxyphenyl)nicotinamide: MS (<i>m/z</i>): 263/265 (M+H) ⁺ ; C ₁₁ H ₁₁ Cl ₁ N ₂ O, requires 262.7.	o-tolyl	3-fluorophenyl	321
6-Chloro-N-methyl-N-phenylnicotinamide: MS (<i>m/z</i>): 247/249 (M+H) ⁺ ; C ₁₁ H ₁₁ Cl ₁ N ₂ O, requires 246.7.	o-tolyl	4-fluorophenyl	321
5-N-Benzyl-6-chloronicotinamide: MS (<i>m/z</i>): 247/249 (M+H) ⁺ ; C ₁₂ H ₁₃ Cl ₁ N ₂ O, requires 246.7.	o-tolyl	2,4-difluorophenyl	339
	o-tolyl	2-methoxyphenyl	333
	o-tolyl	3-methoxyphenyl	333
	o-tolyl	4-methoxyphenyl	333
	o-tolyl	2,4-dimethoxyphenyl	363
	o-tolyl	2-phenoxyphenyl	395
	o-tolyl	2-biphenyl	379
	o-tolyl	3-phenoxyphenyl	395
	o-tolyl	4-phenoxyphenyl	395
	o-tolyl	4-biphenyl	379
	o-tolyl	4-benzylphenyl	393
	o-tolyl	4-(trifluoromethoxy)phenyl	387
	o-tolyl	cyclohexyl	309
	o-tolyl	2-methylcyclohexyl	323
	o-tolyl	cycloheptyl	323
	o-tolyl	indan-1-yl	343
	o-tolyl	2-dicyclononyl	492
	2-fluorophenyl	phenyl	307
	2-fluorophenyl	o-tolyl	321
	2-fluorophenyl	4-chloro-2-methylphenyl	356
	2-fluorophenyl	2-fluorophenyl	325
	2-fluorophenyl	3-fluorophenyl	325
	2-fluorophenyl	4-fluorophenyl	325
	2-fluorophenyl	2,4-difluorophenyl	343
	2-fluorophenyl	2-methoxyphenyl	337
	2-fluorophenyl	3-methoxyphenyl	337
	2-fluorophenyl	4-methoxyphenyl	337

191

192

2-fluorophenyl	2,4-dimethoxyphenyl	367	2,6-dimethylphenyl	4-(trifluoromethoxy)phenyl	401
2-fluorophenyl	2-phenoxyphenyl	399	2,6-dimethylphenyl	cyclohexyl	323
2-fluorophenyl	3-phenoxyphenyl	399	2,6-dimethylphenyl	2-methylcyclohexyl	337
2-fluorophenyl	4-phenoxyphenyl	399	2,6-dimethylphenyl	cycloheptyl	667
2-fluorophenyl	4-biphenyl	383	2,6-dimethylphenyl	indan-1-yl	357
2-fluorophenyl	4-benzylphenyl	397	2,6-dimethylphenyl	2-dicyclohexyl	406
2-fluorophenyl	4-(trifluoromethoxy)phenyl	391	2-phenoxyphenyl	phenyl	381
2-fluorophenyl	cyclohexyl	313	2-phenoxyphenyl	o-tolyl	395
2-fluorophenyl	2-methylcyclohexyl	327	2-phenoxyphenyl	4-chloro-2-methylphenyl	430
2-fluorophenyl	cycloheptyl	327	2-phenoxyphenyl	2-fluorophenyl	399
2-fluorophenyl	indan-1-yl	347	2-phenoxyphenyl	3-fluorophenyl	399
2-fluorophenyl	2-dicyclohexyl	395	2-phenoxyphenyl	4-fluorophenyl	399
2,6-dimethylphenyl	phenyl	317	2-phenoxyphenyl	2,4-difluorophenyl	417
2,6-dimethylphenyl	o-tolyl	331	2-phenoxyphenyl	2-methoxyphenyl	411
2,6-dimethylphenyl	4-chloro-2-methylphenyl	366	2-phenoxyphenyl	3-methoxyphenyl	411
2,6-dimethylphenyl	2-fluorophenyl	335	2-phenoxyphenyl	4-methoxyphenyl	411
2,6-dimethylphenyl	3-fluorophenyl	335	2-phenoxyphenyl	2,4-dimethoxyphenyl	441
2,6-dimethylphenyl	4-fluorophenyl	335	2-phenoxyphenyl	2-phenoxyphenyl	473
2,6-dimethylphenyl	2,4-difluorophenyl	353	2-phenoxyphenyl	3-phenoxyphenyl	473
2,6-dimethylphenyl	2,6-dimethoxyphenyl	347	2-phenoxyphenyl	4-phenoxyphenyl	473
2,6-dimethylphenyl	3-methoxyphenyl	347	2-phenoxyphenyl	4-biphenyl	457
2,6-dimethylphenyl	4-methoxyphenyl	347	2-phenoxyphenyl	4-benzylphenyl	472
2,6-dimethylphenyl	2-methoxyphenyl	347	2-phenoxyphenyl	4-(trifluoromethoxy)phenyl	465
2,6-dimethylphenyl	2,4-dimethoxyphenyl	409	2-phenoxyphenyl	cyclohexyl	387
2,6-dimethylphenyl	3-phenoxyphenyl	409	2-phenoxyphenyl	2-methylcyclohexyl	401
2,6-dimethylphenyl	4-phenoxyphenyl	409	2-phenoxyphenyl	cycloheptyl	401
2,6-dimethylphenyl	4-biphenyl	393	2-phenoxyphenyl	indan-1-yl	421
2,6-dimethylphenyl	4-benzylphenyl	407	2-phenoxyphenyl	2-dicyclohexyl	470

193

phenyl	phenyl	289	2, 4-difluorophenyl	361
phenyl	o-tolyl	303	2, 4-difluorophenyl	355
phenyl	4-chloro-2-methylphenyl	338	2, 4-difluorophenyl	355
phenyl	2-fluorophenyl	307	2, 4-difluorophenyl	355
phenyl	3-fluorophenyl	307	2, 4-difluorophenyl	385
phenyl	4-fluorophenyl	307	2, 4-difluorophenyl	417
phenyl	2, 4-difluorophenyl	325	2, 4-difluorophenyl	401
phenyl	2-methoxyphenyl	319	2, 4-difluorophenyl	417
phenyl	3-methoxyphenyl	319	2, 4-difluorophenyl	417
phenyl	4-methoxyphenyl	319	2, 4-difluorophenyl	415
phenyl	2, 4-dimethoxyphenyl	349	2, 4-difluorophenyl	409
phenyl	2-phenoxyphenyl	381	2, 4-difluorophenyl	331
phenyl	3-phenoxyphenyl	381	2, 4-difluorophenyl	345
phenyl	4-phenoxyphenyl	381	2, 4-difluorophenyl	345
phenyl	4-biphenyl	365	2, 4-difluorophenyl	365
phenyl	4-benzylphenyl	379	2, 4-difluorophenyl	413
phenyl	4-(trifluoromethoxy)phenyl	373	2, 6-diisopropylphenyl phenyl	373
phenyl	cyclohexyl	295	2, 6-diisopropylphenyl o-tolyl	387
phenyl	2-methylcyclohexyl	309	2, 6-diisopropylphenyl 4-chloro-2-methylphenyl	422
phenyl	cycloheptyl	309	2, 6-diisopropylphenyl 2-fluorophenyl	391
phenyl	indan-1-yl	329	2, 6-diisopropylphenyl 3-fluorophenyl	391
phenyl	2-dicyclohexyl	377	2, 6-diisopropylphenyl 4-fluorophenyl	391
phenyl	phenyl	325	2, 6-diisopropylphenyl 2, 4-difluorophenyl	409
phenyl	o-tolyl	339	2, 6-diisopropylphenyl 2-methoxyphenyl	403
phenyl	4-chloro-2-methylphenyl	374	2, 6-diisopropylphenyl 3-methoxyphenyl	403
phenyl	2, 4-difluorophenyl	343	2, 6-diisopropylphenyl 4-methoxyphenyl	403
phenyl	2, 4-difluorophenyl	343	2, 6-diisopropylphenyl 2, 4-dimethoxyphenyl	434
phenyl	4-fluorophenyl	343	2, 6-diisopropylphenyl 2-phenoxyphenyl	466

194

phenyl	phenyl	289	2, 4-difluorophenyl	361
phenyl	o-tolyl	303	2, 4-difluorophenyl	355
phenyl	4-chloro-2-methylphenyl	338	2, 4-difluorophenyl	355
phenyl	2-fluorophenyl	307	2, 4-difluorophenyl	355
phenyl	3-fluorophenyl	307	2, 4-difluorophenyl	385
phenyl	4-fluorophenyl	307	2, 4-difluorophenyl	417
phenyl	2, 4-difluorophenyl	325	2, 4-difluorophenyl	401
phenyl	2-methoxyphenyl	319	2, 4-difluorophenyl	417
phenyl	3-methoxyphenyl	319	2, 4-difluorophenyl	417
phenyl	4-methoxyphenyl	319	2, 4-difluorophenyl	415
phenyl	2, 4-dimethoxyphenyl	349	2, 4-difluorophenyl	409
phenyl	2-phenoxyphenyl	381	2, 4-difluorophenyl	331
phenyl	3-phenoxyphenyl	381	2, 4-difluorophenyl	345
phenyl	4-phenoxyphenyl	381	2, 4-difluorophenyl	345
phenyl	4-biphenyl	365	2, 4-difluorophenyl	365
phenyl	4-benzylphenyl	379	2, 4-difluorophenyl	413
phenyl	4-(trifluoromethoxy)phenyl	373	2, 6-diisopropylphenyl phenyl	373
phenyl	cyclohexyl	295	2, 6-diisopropylphenyl o-tolyl	387
phenyl	2-methylcyclohexyl	309	2, 6-diisopropylphenyl 4-chloro-2-methylphenyl	422
phenyl	cycloheptyl	309	2, 6-diisopropylphenyl 2-fluorophenyl	391
phenyl	indan-1-yl	329	2, 6-diisopropylphenyl 3-fluorophenyl	391
phenyl	2-dicyclohexyl	377	2, 6-diisopropylphenyl 4-fluorophenyl	391
phenyl	phenyl	325	2, 6-diisopropylphenyl 2, 4-difluorophenyl	409
phenyl	o-tolyl	339	2, 6-diisopropylphenyl 2-methoxyphenyl	403
phenyl	4-chloro-2-methylphenyl	374	2, 6-diisopropylphenyl 3-methoxyphenyl	403
phenyl	2, 4-difluorophenyl	343	2, 6-diisopropylphenyl 4-methoxyphenyl	403
phenyl	2, 4-difluorophenyl	343	2, 6-diisopropylphenyl 2, 4-dimethoxyphenyl	434
phenyl	4-fluorophenyl	343	2, 6-diisopropylphenyl 2-phenoxyphenyl	466

195

196

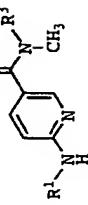
2,6-diisopropylphenyl	3-phenoxyphenyl	466	2,4-dimethoxyphenyl	cyclohexyl	355
2,6-diisopropylphenyl	4-phenoxyphenyl	466	2,4-dimethoxyphenyl	2-methylcyclohexyl	369
2,6-diisopropylphenyl	4-biphenyl	450	3-methoxyphenyl	phenyl	319
2,6-diisopropylphenyl	4-biphenyl	464	3-methoxyphenyl	o-tolyl	333
2,6-diisopropylphenyl	4-(trifluoromethoxy)phenyl	457	3-methoxyphenyl	4-chloro-2-methylphenyl	368
2,6-diisopropylphenyl	cyclohexyl	380	3-methoxyphenyl	2-fluorophenyl	337
2,6-diisopropylphenyl	2-methylcyclohexyl	394	3-methoxyphenyl	3-fluorophenyl	337
2,6-diisopropylphenyl	cycloheptyl	394	3-methoxyphenyl	4-fluorophenyl	337
2,6-diisopropylphenyl	indan-1-yl	414	3-methoxyphenyl	2,4-difluorophenyl	355
2,6-diisopropylphenyl	2-dicyclohexyl	462	3-methoxyphenyl	2-methoxyphenyl	349
2,6-diisopropylphenyl	phenyl	349	3-methoxyphenyl	3-methoxyphenyl	349
2,4-dimethoxyphenyl	o-tolyl	363	3-methoxyphenyl	4-methoxyphenyl	349
2,4-dimethoxyphenyl	4-chloro-2-methylphenyl	398	3-methoxyphenyl	2,4-dimethoxyphenyl	379
2,4-dimethoxyphenyl	2-fluorophenyl	367	3-methoxyphenyl	2-phenoxyphenyl	411
2,4-dimethoxyphenyl	3-fluorophenyl	367	3-methoxyphenyl	3-phenoxyphenyl	411
2,4-dimethoxyphenyl	4-fluorophenyl	367	3-methoxyphenyl	4-phenoxyphenyl	411
2,4-dimethoxyphenyl	4-biphenyl	385	3-methoxyphenyl	4-biphenyl	395
2,4-dimethoxyphenyl	2-methoxyphenyl	379	3-methoxyphenyl	4-biphenyl	409
2,4-dimethoxyphenyl	3-methoxyphenyl	379	3-methoxyphenyl	4-(trifluoromethoxy)phenyl	403
2,4-dimethoxyphenyl	4-methoxyphenyl	379	3-methoxyphenyl	3-trifluoromethylphenyl	387
2,4-dimethoxyphenyl	409	3-methoxyphenyl	cyclohexyl	625	
2,4-dimethoxyphenyl	2,4-dimethoxyphenyl	441	3-methoxyphenyl	2-methylcyclohexyl	339
2,4-dimethoxyphenyl	2-phenoxyphenyl	441	4-methoxyphenyl	phenyl	319
2,4-dimethoxyphenyl	3-phenoxyphenyl	441	4-methoxyphenyl	o-tolyl	333
2,4-dimethoxyphenyl	4-phenoxyphenyl	441	4-methoxyphenyl	4-chloro-2-methylphenyl	368
2,4-dimethoxyphenyl	4-biphenyl	425	4-methoxyphenyl	2-fluorophenyl	337
2,4-dimethoxyphenyl	4-benzylphenyl	439	4-methoxyphenyl	3-fluorophenyl	337
2,4-dimethoxyphenyl	4-(trifluoromethoxy)phenyl	433	4-methoxyphenyl	4-fluorophenyl	337
2,4-dimethoxyphenyl	3-trifluoromethylphenyl	417	4-methoxyphenyl	4-fluorophenyl	337

197

4-methoxyphenyl	2, 4-difluorophenyl
4-methoxyphenyl	2-methoxyphenyl
4-methoxyphenyl	3-methoxyphenyl
4-methoxyphenyl	4-methoxyphenyl
4-methoxyphenyl	2, 4-dimethoxyphenyl
4-methoxyphenyl	2-phenoxyphenyl
4-methoxyphenyl	3-phenoxyphenyl
4-methoxyphenyl	4-phenoxyphenyl
4-methoxyphenyl	4-biphenyl
4-methoxyphenyl	4-benzylphenyl
4-methoxyphenyl	4-(trifluoromethoxy)phenyl
4-methoxyphenyl	3-trifluoromethylphenyl
4-methoxyphenyl	cyclohexyl
4-methoxyphenyl	2-methylcyclohexyl
4-methoxyphenyl	phenyl
2-methoxyphenyl	o-tolyl
2-methoxyphenyl	4-chloro-2-methylphenyl
2-methoxyphenyl	2-fluorophenyl
2-methoxyphenyl	3-fluorophenyl
2-methoxyphenyl	4-fluorophenyl
2-methoxyphenyl	2, 4-difluorophenyl
2-methoxyphenyl	2-methoxyphenyl
2-methoxyphenyl	3-methoxyphenyl
2-methoxyphenyl	4-methoxyphenyl
2-methoxyphenyl	2, 4-dimethoxyphenyl
2-methoxyphenyl	2-phenoxyphenyl
2-methoxyphenyl	3-phenoxyphenyl
2-methoxyphenyl	4-phenoxyphenyl
2-methoxyphenyl	4-biphenyl
2-methoxyphenyl	4-benzylphenyl
2-methoxyphenyl	4-(trifluoromethoxy)phenyl
2-methoxyphenyl	3-trifluoromethylphenyl
2-methoxyphenyl	cyclohexyl
2-methoxyphenyl	2-methylcyclohexyl
2-methoxyphenyl	phenyl

2-methoxyphenyl	4-biphenyl	395
2-methoxyphenyl	4-benzylphenyl	409
2-methoxyphenyl	4-(trifluoromethoxy)phenyl	403
2-methoxyphenyl	3-trifluoromethylphenyl	387
2-methoxyphenyl	cyclohexyl	625
2-methoxyphenyl	2-methylcyclohexyl	139

Table 9



MS	R	R	m/z
387			
625	4-chlorophenyl	phenyl	338
339	4-chlorophenyl	o-tolyl	352
319	4-chlorophenyl	4-chloro-2-methylphenyl	386
333	4-chlorophenyl	2-fluorophenyl	356
368	4-chlorophenyl	3-fluorophenyl	356
337	4-chlorophenyl	4-fluorophenyl	356
337	4-chlorophenyl	2,4-difluorophenyl	374
337	4-chlorophenyl	2-methoxyphenyl	368
355	4-chlorophenyl	3-methoxyphenyl	368
349	4-chlorophenyl	4-methoxyphenyl	368
349	4-chlorophenyl	2,4-dimethoxyphenyl	398
349	4-chlorophenyl	2-phenoxyphenyl	430
379	4-chlorophenyl	3-phenoxyphenyl	430
411	4-chlorophenyl	4-phenoxyphenyl	430
411	4-chlorophenyl	4-biphenyl	411

MS

338	352	386	356	356	356	374	368	368	368	398	430	430	430	414
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

4-benzylphenyl

661

200

Table 1C

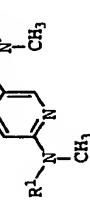


		R ¹	R ²	m/z
phenyl	o-tolyl	317		
phenyl	4-chloro-2-methylphenyl	352		
phenyl	2-fluorophenyl	321	o-tolyl	317
phenyl	3-fluorophenyl	321	o-tolyl	352
phenyl	4-fluorophenyl	321	o-tolyl	323
phenyl	2,4-difluorophenyl	339	2-fluorophenyl	321
phenyl	2-methoxyphenyl	333	2-fluorophenyl	356
phenyl	3-methoxyphenyl	333	2-fluorophenyl	327
phenyl	4-methoxyphenyl	333	2,6-dimethylphenyl	331
phenyl	2,4-dimethoxyphenyl	363	2,6-dimethylphenyl	366
phenyl	2-phenoxyphenyl	395	2,6-dimethylphenyl	337
phenyl	3-phenoxyphenyl	395	2-phenoxyphenyl	395
phenyl	4-phenoxyphenyl	395	2-phenoxyphenyl	430
phenyl	4-biphenyl	379	2-phenoxyphenyl	401
phenyl	4-benzylphenyl	393	phenyl	303
phenyl	4-(trifluoromethoxy)phenyl	387	phenyl	338
phenyl	3-trifluoromethylphenyl	371	phenyl	309
phenyl	cyclohexyl	309	2,4-difluorophenyl	339
phenyl	2-methylcyclohexyl	323	2,4-difluorophenyl	345
			2,6-diisopropylphenyl	N-methylphenyl
			2,6-diisopropylphenyl	4-chloro-N-methylphenyl
			2,6-diisopropylphenyl	N-methylcyclohexyl

201

2, 4-dimethoxyphenyl	N-methylphenyl	163
2, 4-dimethoxyphenyl	4-chloro-N-methylphenyl	398
2, 4-dimethoxyphenyl	N-methyl[cyclo]hexyl	369
3-methoxyphenyl	N-methylphenyl	333
3-methoxyphenyl	4-chloro-N-methylphenyl	368
3-methoxyphenyl	N-methyl[cyclo]hexyl	339
4-methoxyphenyl	N-methylphenyl	333
4-methoxyphenyl	4-chloro-N-methylphenyl	368
4-methoxyphenyl	N-methyl[cyclo]hexyl	339
2-methoxyphenyl	N-methylphenyl	333
2-methoxyphenyl	4-chloro-N-methylphenyl	368
2-methoxyphenyl	N-methyl[cyclo]hexyl	339

Table 11



R'	R''	MS (m/z)
-chlorophenyl	phenyl	352
-chlorophenyl	4-chlorophenyl	386
-chlorophenyl	cyclohexyl	358
phenyl	phenyl	317
phenyl	4-chlorophenyl	352
phenyl	cyclohexyl	323

6

The compounds listed in tables 12-13 can be prepared from 6-chloro-N-substituted nicotinamides

compounds and the appropriate amine according to the general procedure above.

Table 12



R_X	R_Y
o-tolyl	3-trifluoromethylphenyl
2-fluorophenyl	3-trifluoromethylphenyl
2, 6-dimethylphenyl	3-trifluoromethylphenyl
2-phenoxyphenyl	3-trifluoromethylphenyl
phenyl	3-trifluoromethylphenyl
2, 4-difluorophenyl	3-trifluoromethylphenyl
2, 6-disopropylphenyl	3-trifluoromethylphenyl
2, 4-dimethoxyphenyl	cycloheptyl
2, 4-dimethoxyphenyl	indan-1-yl
2, 4-dimethoxyphenyl	2-dicyclohexyl
3-methoxyphenyl	cycloheptyl
3-methoxyphenyl	indan-1-yl
3-methoxyphenyl	2-dicyclohexyl
4-methoxyphenyl	cycloheptyl
4-methoxyphenyl	indan-1-yl
4-methoxyphenyl	2-dicyclohexyl
2-methoxyphenyl	cycloheptyl
2-methoxyphenyl	indan-1-yl
2-methoxyphenyl	2-dicyclohexyl

205

ng/ml lipopolysaccharide from *E. coli* K532 were added to each well. Cells were cultured an additional 4 hrs. Culture supernatants were then removed and TNF presence in the supernatants was quantified using an ELISA.

5

TNF ELISA

Flat bottom, 96 well Corning High Binding ELISA plates were coated overnight (4°C) with 150 µl/well of 3 µg/ml murine anti-human TNF- α MAb (R&D Systems #MAB210). Wells were then blocked for 1 hr at room temperature with 200 µl/well of CaCl₂-free ELISA buffer supplemented to contain 20 mg/ml BSA (standard ELISA buffer: 20 mM, 150 mM NaCl, 2 mM CaCl₂, 0.15 mM thimerosal, pH 7.4).

Plates were washed and replenished with 100 µl of test supernatants (diluted 1:3) or standards. Standards consisted of eleven 1.5-fold serial dilutions from a stock of 1 ng/ml recombinant human TNF (R&D Systems). Plates were incubated at room temperature for 1 hr on orbital shaker (300 rpm), washed and replenished with 100 µl/well of 0.5 µg/ml goat anti-human TNF- α (R&D systems #AB-210-NA) biotinylated at a 4:1 ratio. Plates were incubated for 40 min, washed and replenished with 100 µl/well of alkaline phosphatase-conjugated streptavidin (Jackson ImmunoResearch #016-050-084) at 0.02 µg/ml. Plates were incubated 30 min, washed and replenished with 200 µl/well of 1 mg/ml of p-nitrophenyl phosphate. After 30 min, plates were read at 405 nm on a Vmax plate reader.

30

Data analysis

Standard curve data were fit to a second order polynomial and unknown TNF- α concentrations determined from their OD by solving this equation for concentration. TNF concentrations were then plotted vs. test compound concentration using a second order polynomial. This equation was then used to calculate

206

the concentration of test compounds causing a 50% reduction in TNF production.

The following compounds had an IC₅₀ of less than 15

5 μ M:

- 2-cyclohexyloxy-5-(2-chlorophenylcarbonylamino)pyridine;
- 2-cyclohexyloxy-5-(2-methylphenylcarbonylamino)pyridine;
- 2-cyclohexyloxy-5-(2,6-dichlorophenylcarbonylamino)pyridine;
- 10 2-cyclohexyloxy-5-(2,6-dimethylphenylcarbonylamino)pyridine;
- 2-(2,4-dimethylphenoxy)-5-(2-methylphenylcarbonylamino)pyridine;
- 2-(2-methyl-4-fluorophenoxy)-5-(2-methylphenylcarbonylamino)pyridine;
- 15 2-(2-methyl-4-chlorophenoxy)-5-(2-chlorophenylcarbonylamino)pyridine;
- 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine;
- 20 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;
- 2-(2-methyl-4-fluorophenoxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine;
- 25 2-(2-methyl-4-fluorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;
- 30 2-(2,4-dimethylphenylcarbonylamino)pyridine;
- 2-(1-naphthyl)oxy-5-(2,6-dichlorophenylcarbonylamino)pyridine;
- 35 2-(1-naphthyl)oxy-5-(2,6-dichlorophenylcarbonylamino)pyridine;

207

208

2-(2-methyl-4-chlorophenoxy)-5-(3,5-dimethyl-4-isoxazolyl)carbonylamino)pyridine;

2-cyclohexylamino-5-(2,6-dichlorophenylcarbonylamino)pyridine;

5 2-cyclohexylamino-5-(2,6-dimethylphenylcarbonylamino)pyridine;

2-(2-methylcyclohexylamino)-5-(2,6-dichlorophenylcarbonylamino)pyridine;

10 2-(2-methylcyclohexylamino)-5-(2-methylphenylcarbonylamino)pyridine;

2-(2-methylphenylamino)-5-(2-methylphenylcarbonylamino)pyridine;

15 2-(2-methylphenylamino)-5-(2-methylphenylcarbonylcarbonylamino)pyridine; and

2-(2-methyl-4-chlorophenylamino)-5-(2-methylphenylaminocarbonyl)pyridine.

20 Compounds of the invention can also be shown to inhibit LPS-induced release of IL-1 β , IL-6 and/or IL-8 from monocytes by measuring concentrations of IL-1 β , IL-6 and/or IL-8 by methods well known to those skilled in the art. In a similar manner to the above described assay involving the LPS induced release of TNF- α from monocytes, compounds of this invention can also be shown to inhibit LPS induced release of IL-1 β , IL-6 and/or IL-8 from monocytes by measuring concentrations of IL-1 β , IL-6 and/or IL-8 by methods well known to those skilled in the art. Thus, the compounds of the invention may lower elevated levels of TNF- α , IL-1, IL-6, and IL-8 levels. Reducing elevated levels of these inflammatory cytokines to basal levels or below is favorable in controlling, slowing progression, and alleviating many disease states. All of the compounds are useful in the methods of treating disease states in which TNF- α , IL-

1 β , IL-6, and IL-8 play a role to the full extent of the definition of TNF- α -mediated diseases described herein.

Inhibition of LPS-induced TNF- α production in mice

5 Male DBA/1LACJ mice are dosed with vehicle or test compounds in a vehicle (the vehicle consisting of 0.5% tragacanth in 0.03 N HCl) 30 minutes prior to lipopolysaccharide (2 mg/kg, I.V.) injection. Ninety minutes after LPS injection, blood are collected and the serum is analyzed by ELISA for TNF levels.

10 Selected compounds from the class have shown in vivo activity in a LPS mouse model in which serum levels of TNF- α were reduced in the presence of compounds of this invention.

15 Compounds of the invention may be shown to have anti-inflammatory properties in animal models of inflammation, including carageenan paw edema, collagen induced arthritis and adjuvant arthritis, such as the carageenan paw edema model (C. A. Winter et al Proc. Soc. Exp. Biol. Med. (1962) vol 111, p 544; K. F. Swingle, in R. A. Scherrer and M. W. Whitehouse, Eds., *Antiinflammatory Agents, Chemistry and Pharmacology*, Vol. 13-II, Academic, New York, 1974, p. 33) and collagen induced arthritis (D. E. Trentham et al J. Exp. Med. (1977) vol. 146, p 857; J. S. Courtenay, *Nature* (New Biol.) (1980), Vol 283, p 666).

^{35}I -Glucagon Binding Screen with CHO/KMGLUR Cells

10 The assay is described in WO 97/16442, which is incorporated herein by reference in its entirety.

Reagents

15 The reagents can be prepared as follows: (a) prepare fresh 1M o-phenanthroline (Aldrich) (198.2 mg/ml ethanol); (b) prepare fresh 0.5M DTT (Sigma); (c) Protease Inhibitor Mix (1000X): 5 mg leupeptin, 10 mg

209

benzamidine, 40 mg bacitracin and 5 mg soybean trypsin inhibitor per ml DMSO and store aliquots at -20°C; (d) 250 μ M human glucagon (Peninsula): solubilize 0.5 mg vial in 575 μ l 0.1N acetic acid (1 μ l yields 1 μ M final concentration in assay for non-specific binding) and store in aliquots at -20°C; (e) Assay Buffer: 20mM Tris (pH 7.8), 1 mM DTT and 3 mM o-phenanthroline; (f) Assay Buffer with 0.1% BSA (for dilution of label only: 0.01% final in assay): 10 μ l 10% BSA (heat-inactivated) and 990 μ l Assay Buffer; (g) 125 I-Glucagon (NEN, receptor-grade, 2200 Ci/mmol): dilute to 50,000 cpm/25 μ l in assay buffer with BSA (about 50 μ M final concentration in assay).

15 Harvesting of CHO/hGLUR Cells for Assay

1. Remove media from confluent flask then rinse once each with PBS (Ca, Mg-free) and Enzyme-free Dissociation Fluid (Specialty Media, Inc.).
2. Add 10 ml Enzyme-free Dissoc. Fluid and hold for about 4 min. at 37°C.
3. Gently tap cells free, triturate, take aliquot for counting and centrifuge remainder for 5 min. at 1000 rpm.
4. Resuspend pellet in Assay Buffer at 75000 cells per 100 μ l.

25 Membrane preparations of CHO/hGLUR cells can be used in place of whole cells at the same assay volume. Final protein concentration of a membrane preparation is determined on a per batch basis.

30 Assay

The determination of inhibition of glucagon binding can be carried out by measuring the reduction of I^{125} -glucagon binding in the presence of compounds of Formula 35 I. The reagents are combined in 120 μ l of assay buffer as follows:

210

	Compound/ Vehicle	250 μ M Glucagon	125 I- Glucagon	CHO/hGLUR Cells
Total	-/5 μ l	--	25 μ l	100 μ l
Binding				
+	5 μ l/--	--	25 μ l	100 μ l
Compound				
Nonspecific	-/5 μ l	1 μ l	25 μ l	100 μ l
ir				
Binding				

The mixture is incubated for 60 min. at 22°C on a shaker at 275 rpm. The mixture is filtered over pre-soaked 5 (0.5% polyethylimine (PEI)) GF/C filtermat using an Imnotech Harvester or Tomtec Harvester with four washes of ice-cold 20mM Tris buffer (pH 7.8). The radioactivity in the filters is determined by a gamma-scintillation counter.

10 Thus, compounds of the invention may also be shown to inhibit the binding of glucagon to glucagon receptors.

15 Cyclooxygenase Enzyme Activity Assay

15 The human monocytic leukemia cell line, THP-1, differentiated by exposure to phorbol esters expresses only COX-1; the human osteosarcoma cell line 143B expresses predominantly COX-2. THP-1 cells are routinely cultured in RPMI complete media supplemented with 10% FBS and human osteosarcoma cells (ROSC) are cultured in minimal essential media supplemented with 10% fetal bovine serum (MEM-10%FBS); all cell incubations are at 37°C in a humidified environment containing 5% CO₂.

25 COX-1 Assay

In preparation for the COX-1 assay, THP-1 cells are grown to confluence, split 1:3 into RPMI containing 2%

211

212

FBS and 10 mM phorbol 12-myristate 13-acetate (TPA), and incubated for 48 hours on a shaker to prevent attachment. Cells are pelleted and resuspended in Hank's Buffered Saline (HBS) at a concentration of 2.5 x 10⁶ cells/mL and plated in 96-well culture plates at a density of 5 x 10³ cells/mL. Test compounds are diluted in HBS and added to the desired final concentration and the cells are incubated for an additional 4 hours. Arachidonic acid is added to a final concentration of 30 mM, the cells incubated for 20 minutes at 37°C, and enzyme activity determined as described below.

COX-2 Assay

For the COX-2 assay, subconfluent HOSC are trypsinized and resuspended at 3 x 10⁶ cells/mL in MEM-FBS containing 1 mg human IL-1b/mL, plated in 96-well tissue culture plates at a density of 3 x 10³ cells per well, incubated on a shaker for 1 hour to evenly distribute cells, followed by an additional 2 hour static incubation to allow attachment. The media is then replaced with MEM containing 2% FBS (MEM-2%FBS) and 1 ng human IL-1b/mL, and the cells incubated for 18-22 hours. Following replacement of media with 190 mL MEM, 10 mL of test compound diluted in HBS is added to 10 achieve the desired concentration and the cells incubated for 4 hours. The supernatants are removed and replaced with MEM containing 30 mM arachidonic acid, the cells incubated for 20 minutes at 37°C, and enzyme activity determined as described below.

COX Activity Determined

After incubation with arachidonic acid, the reactions are stopped by the addition of 1 N HCl, followed by neutralization with 1 N NaOH and centrifugation to pellet cell debris. Cyclooxygenase enzyme activity in both HOSC and THP-1 cell supernatants

is determined by measuring the concentration of PGE₂ using a commercially available ELISA (Neogen #40110). A standard curve of PGE₂ is used for calibration, and commercially available COX-1 and COX-2 inhibitors are included as standard controls.

The following compound exhibits activities in the Cyclooxygenase assay with IC₅₀ values of 10 μ M or less: 2-(2,4-dimethylphenylamino)-5-(2,6-dichlorophenylcarbonyl)amino)pyridine.

Raf Kinase assay

In vitro Raf kinase activity is measured by the extent of phosphorylation of the substrate MEK (Map kinase/ERK kinase) by activated Raf kinase. Phosphorylated MEK is trapped on a filter and incorporation of radiolabeled phosphate is quantified by scintillation counting.

MATERIALS:

20 Activated Raf is produced by triple transfection of SF9 cells with baculoviruses expressing "Glu-Glu"-epitope tagged Raf, val¹⁴-H-Ras, and Lck. The "Glu-Glu"-epitope, Glu-Try-Met-Pro-Met-Glu, was fused to the carboxy-terminus of full length c-Raf. Catalytically inactive MEK (K97A mutation) is produced in SF9 cells transfected with a baculovirus expressing c-terminus "Glu-Glu" epitope-tagged K97A MEK1. Anti "Glu-Glu" antibody was purified from cells grown as described in: Grussendorfer, et al., Proceedings of the National Academy of Science, U.S.A. pp 7952-7954, 1985. Column buffer: 20 mM Tris pH=8, 100 mM NaCl, 1 mM EDTA, 2.5 mM EGTA, 10 mM MgCl₂, 2 mM DTT, 0.4 mM AEBSF, 0.1% n-octylglucopyranoside, 1 mM okadaic acid, and 10 μ g/mL 35 each of benzamidine, leupeptin, pepstatin, and aprotinin.

213

5x Reaction buffer: 125 mM HEPES pH=8, 25 mM MgCl₂, 5 mM EDTA, 5 mM Na₂VO₄, 100 µg/mL BSA.
 Enzyme dilution buffer: 25 mM HEPES pH=8, 1 mM EDTA, 1 mM Na₂VO₄, 400 µg/mL BSA.
 Stop solution: 100 mM EDTA, 80 mM sodium pyrophosphate.
 Filter plates: Millipore multiscreen # SE3MM078E3, Immobilon-P (PVDF).

METHODS:

10 Protein purification: Sf9 cells were infected with baculovirus and grown as described in Williams, et al., Proceedings of the National Academy of Science, U.S.A. pp 2922-2926, 1992. All subsequent steps were preformed on ice or at 4 °C. Cells were pelleted and lysed by sonication in column buffer. Lysates were spun at 17,000xg for 20 min, followed by 0.22 µm filtration. Epitope tagged proteins were purified by chromatography over GammaBind Plus affinity column to which the "Glu-Glu" antibody was coupled. Proteins were loaded on the column followed by sequential washes with two column volumes of column buffer, and eluted with 50 µg/mL Glu-Tyr-Met-Pro-Met-Glu in column buffer.

15 Raf kinase assay: Test compounds were evaluated using ten 3-fold serial dilutions starting at 10 - 100 µM. 10 µL of the test inhibitor or control, dissolved in 10% DMSO, was added to the assay plate followed by the addition of 30 µL of the a mixture containing 10 µL 5x reaction buffer, 1mM 33P-γ-ATP (20 µCi/mL), 0.5 µL MEX (2.5 mg/mL), 1 µL 50 mM β-mercaptoethanol. The reaction was started by the addition of 10 µL of enzyme dilution buffer containing 1 mM DTT and an amount of activated Raf that produces linear kinetics over the reaction time course. The reaction was mixed and incubated at room

214

temperature for 90 min. and stopped by the addition of 50 µL stop solution. 90 µL aliquots of this stopped solution were transferred onto GFP-30 cellulose microtiter filter plates (Polyfiltrronics), the filter places washed in four well volumes of 5% phosphoric acid, allowed to dry, and then replenished with 25 µL scintillation cocktail. The plates were counted for ³³P gamma emission using a TopCount scintillation Reader.

Accordingly, the compounds of the invention or a pharmaceutical composition thereof are useful for prophylaxis and treatment of rheumatoid arthritis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic & cell destruction; osteoarthritis; 5 rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; Reiter's syndrome; type I and type II diabetes; bone resorption diseases; graft vs. host reaction; ischemia reperfusion injury; atherosclerosis; brain trauma; Alzheimer's disease; stroke; myocardial infarction; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. 10 HTV-1, HRV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster, all of which are sensitive to TNF-α and/or IL-1 inhibition or glucagon antagonism, will also be positively effected by the compounds and methods of the invention.

The compounds of the present invention may also possess oncolytic characteristics and may be useful for the treatment of cancer. The compounds of the present invention may also block signal transduction by 15 extracellular mitogenic stimuli and oncoproteins through inhibition of Raf kinase.

35

The compounds of the present invention also may possess analgesic properties and may be useful for the treatment of pain disorders, such as hyperalgesia due to excessive IL-1. The compounds of the present invention may also prevent the production of prostaglandins by inhibition of enzymes in the human arachidonic acid/prostaglandin pathway, including cyclooxygenase (WO 96/03387, incorporated herein by reference in its entirety).

10 Because of their ability to lower TNF- α and IL-1 concentrations or inhibit glucagon binding to its receptor, the compounds of the invention are also useful research tools for studying the physiology associated with blocking these effects.

15 The methods of the invention comprise administering an effective dose of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either, to a subject (i.e., an animal, preferably a mammal, most preferably a human) in need of

20 a reduction in the level of TNF- α , IL-1, IL-6, and/or IL-8 levels and/or reduction in plasma glucose levels and/or which subject may be suffering from rheumatoid arthritis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous

25 leukemia; pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis;

30 asthma; muscle degeneration; cachexia; Reiter's syndrome; type I and type II diabetes; cancer; bone resorption diseases; graft vs. host reaction; Alzheimer's disease; stroke; myocardial infarction; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection, or which subject is infected by HIV-1,

HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), or herpes zoster.

In another aspect, this invention comprises the use 5 of a compound of the invention, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment either acutely or

chronically of a TNF- α , IL-1 β , IL-6, and/or IL-8 mediated disease state, including those described previously. The compounds of the present are also useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent signal transduction by extracellular mitogenic stimuli and oncoproteins through inhibition of Raf kinase.

Also, the compounds of this invention are useful in the manufacture of a analgesic medicament and a medicament for treating pain disorders, such as hyperalgesia. The compounds of the present invention also are useful in the manufacture of a medicament to prevent the production of prostaglandins by inhibition of enzymes in the human arachidonic acid/prostaglandin pathway.

In still another aspect, this invention provides a pharmaceutical composition comprising an effective TNF- α , IL-1 β , IL-6, and/or IL-8 lowering amount and/or effective plasma glucose level lowering amount, and/or effective tumor suppressing amount of a compound of the invention and a pharmaceutically acceptable carrier or diluent, and if desired other active ingredients. The compounds of the invention are administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended.

Therapeutically effective doses of the compounds of the present invention required to arrest the progress or prevent tissue damage associated with the disease are 35

readily ascertained by one of ordinary skill in the art using standard methods.

For the treatment of TNF- α , IL-1 β , IL-6, and IL-8 mediated diseases, cancer, and/or hyperglycemia, the compounds of the present invention may be administered orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or intraperitoneally.

The dosage regimen for treating a TNF- α , IL-1, IL-6, and IL-8 mediated diseases, cancer, and/or hyperglycemia with the compounds of this invention and/or compositions of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an

amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg

administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it 5 may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, 10 ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants 15 appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alcanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric 20 acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water,

25 polyethylene glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be made up in a solid form (including granules, powders or 30 suppositories) or in a liquid form (e.g., solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected to conventional

pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

5 Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also 10 comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

15 Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

20 Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. 25 The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltauritic, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these 30 salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of

221

the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanspropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methansulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diethyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

222

Examples of acids that may be employed to from pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as 5 oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

While the compounds of the invention can be 10 administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are 15 given at the same time or different times, or the therapeutic agents can be given as a single composition. The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which 20 are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics 25 of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, hydroxy, hydroxylalkyl, thiol, alkylthiol, alkylsulfinyl, alkylsulfonyl, alkyl, alkoxyalkyl, cyano, azido, nitro, carboxy, alkoxy carbonyl, aminocarbonyl, 5 alkylaminocarbonyl or dialkylaminocarbonyl radical.

2. The compound of Claim 1 or a pharmaceutically acceptable salt thereof, wherein R¹ is a cycloalkyl, aryl, heterocyclyl or heteroaryl radical which is optionally substituted by 1-4 radicals of C₁-C₆ alkyl, halo, C₁-C₆ haloalkyl of 1-3 halo radicals, cyano, azido, nitro, amidino, R¹⁸-Z¹⁸- or R¹⁸-Z¹⁸-C₆ alkyl; provided that the total number of aryl, heteroaryl, cycloalkyl and heterocyclyl radicals in R¹ is 1-3; and provided when Y is -NR⁴-C(O)-R³, S, R¹ is other than a 2-pyrimidinyl radical;
- 20 R² is a hydrogen or C₁-C₄ alkyl radical; R³ is an aryl or heteroaryl radical which is optionally substituted by 1-5 radicals of C₁-C₆ alkyl, halo, C₁-C₆ haloalkyl of 1-3 halo radicals, cyano, azido, nitro, amidino, R¹⁹-Z¹⁹- or R¹⁹-Z¹⁹-C₁-C₄ alkyl; provided that the total number of aryl and heteroaryl radicals in R³ is 1-3; and provided when Y is -C(O)-NR⁴R⁴, R⁴ is other than a phenyl or naphthyl having an amino, nitro, cyano, carboxy or alkoxy carbonyl substituent bonded to the ring carbon atom adjacent to the ring carbon atom bonded to -NR⁴-; and

R⁴ is a radical of hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ haloalkyl of 1-3 halo radicals, C₂-C₆ haloalkenyl of 1-3 halo radicals, aryl, heteroaryl, aryl-C₁-C₄ alkyl, heteroaryl-C₁-C₄ alkyl or R²⁰-Z²⁰-C₁-C₄ alkyl radical; and

- 5 wherein R¹⁸, R¹⁹ and R²⁰ are each independently a hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl of 1-3 halo radicals, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical; wherein the aryl and heteroaryl radicals of R¹⁸, R¹⁹ and R²⁰ are optionally substituted by 1-3 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, C₁-C₅ alkanoylamino, C₁-C₄ alkylsulfonylamino, C₁-C₄ alkylsulfamyl, C₁-C₄ alkylsulfonyl, (C₁-C₄ alkoxy)carbonylamino, (C₁-C₄ alkoxy)carbonyl, cyano, halo, azido, C₁-C₄ alkyl, C₁-C₄ haloalkyl of 1-3 halo radicals or C₁-C₄ haloalkoxy of 1-3 halo radicals; and
- 10 20 each R²¹ is independently a hydrogen or C₁-C₄ alkyl radical;
- 15 25 R⁵ and R⁶ are each independently a hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl of 1-3 halo radicals, C₁-C₄ haloalkoxy of 1-3 halo radicals, C₁-C₄ aminoalkyl, (C₁-C₄ alkyl)amino-C₁-C₄ alkyl, di(C₁-C₄ alkyl)amino-C₁-C₄ alkyl, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylaminosulfonyl, di(C₁-C₄ alkyl)aminosulfonyl, hydroxy, C₁-C₄ hydroxylalkyl, thiol, C₁-C₄ alkylthiol, C₁-C₄ alkylsulfuryl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkoxy, (C₁-C₄ alkoxy)C₁-C₄ alkyl,

cyano, azido, nitro, carboxy, (C₁-C₄ alkoxyl)carbonyl, aminocarbonyl, (C₁-C₄ alkyl)aminocarbonyl or di(C₁-C₄ alkyl)aminocarbonyl radical; and

5 R' is a hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl of 1-3 halo radicals, C₁-C₄ aminoalkyl, (C₁-C₄ alkyl)amino-C₁-C₄ alkyl, di(C₁-C₄ alkyl)amino-C₁-C₄ aminosulfonyl, C₁-C₄ alkylaminosulfonyl, di(C₁-C₄ alkyl)aminosulfonyl,

10 hydroxy, C₁-C₄ hydroxylalkyl, thiol, C₁-C₄ alkylthiol, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkoxyl, (C₁-C₄ alkoxyl)C₁-C₄ alkyl, cyano, azido, nitro, carboxy, (C₁-C₄ alkoxyl)carbonyl, aminocarbonyl, (C₁-C₄ alkyl)aminocarbonyl or di(C₁-C₄ alkyl)aminocarbonyl

15 radical; and

wherein cycloalkyl is a monocyclic, bicyclic or tricyclic carbocyclic alkyl radical of 5-12 ring members, which is optionally partially unsaturated,

20 benzo fused or heterocyclo fused; aryl is a phenyl or biphenyl radical which is optionally benzo fused or heterocyclo fused; heterocyclyl is a radical of a monocyclic or bicyclic saturated heterocyclic ring system having 5-8 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally partially unsaturated or benzo-fused

25 and optionally substituted by 1-2 oxo or thioxo radicals; and heteraryl is a monocyclic or bicyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally benzo-fused or saturated C₃-C₄-carbocyclic-fused.

5 X is O or NR²;

R' is a cycloalkyl, aryl, heterocyclyl or heteroaryl radical which is optionally substituted by 1-4 radicals of C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl of 1-3 halo radicals, cyano, azido, nitro, amidino, R¹⁸-Z¹⁸- or R¹⁸-Z¹⁸-C₁-C₄ alkyl; provided that the total number of aryl, heteroaryl, cycloalkyl and heterocyclyl radicals in R' is 1-2;

15 wherein each R¹⁸ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₂ alkyl or heteroaryl-C₁-C₂ alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted

20 by 1-2 radicals of hydroxy, C₁-C₄ alkoxyl, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, acetylamino, cyano, halo, azido, C₁-C₄ alkyl, trifluoromethyl or trifluoromethoxy; and

25 R' is a hydrogen or C₁-C₂ alkyl radical;

R³ is an aryl or heteroaryl radical which is optionally substituted by 1-5 radicals of C₁-C₆ alkyl, halo, C₁-C₄ haloalkyl of 1-3 halo radicals, cyano, azido, nitro, amidino, R¹⁹-Z¹⁹- or R¹⁹-Z¹⁹-C₁-C₄ alkyl; provided that the total number of aryl and heteroaryl radicals in R³ is 1-

35 2; and

3. The compound of Claim 2 or a pharmaceutically acceptable salt thereof², wherein Y is -NR⁴-C(O)-R³.

229

wherein each R^{19} is independently a hydrogen, C_1-C_4 alkyl, trifluoromethyl, aryl, heteroaryl, aryl, heteroaryl, $aryl-O_1-C_4$ alkyl or heteroaryl- C_1-C_4 alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkylthiol, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, acetylamino, cyano, halo, C_1-C_4 alkyl, trifluoromethyl or trifluoromethoxy; and

10 R^4 is a radical of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, aryl- C_1-C_4 alkyl, heteroaryl- C_1-C_4 alkyl or $R^{20}-Z^{20}-C_2-C_4$ alkyl radical; and

15 wherein R^{20} is a hydrogen, C_1-C_4 alkyl, aryl, heteroaryl, $aryl-C_1-C_2$ alkyl or heteroaryl- C_1-C_2 alkyl radical; wherein the aryl and heteroaryl radicals of R^4 and R^{20} are optionally substituted by 1-2 radicals of hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkylthiol, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, acetylamino, halo, C_1-C_4 alkyl, trifluoromethyl or trifluoromethoxy; and

Z^{20} is $-O-$ or $-NR^{21}-$; wherein each R^{21} is independently a hydrogen or methyl radical;

25 R^5 and R^6 are each independently a hydrogen, C_1-C_4 alkyl, halo, trifluoromethyl, trifluoromethoxy, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, C_1-C_5 alkanoylamino, hydroxy, C_1-C_4 hydroxalkyl, C_1-C_4 alkoxy, cyano, azido, nitro, carboxy, (C₁-C₄) alkoxy carbonyl, aminocarbonyl, (C₁-C₄) alkyl aminocarbonyl or di(C₁-C₄) alkyl aminocarbonyl radical; and

30 wherein

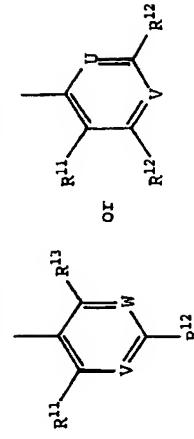
230

R^7 is a hydrogen, C_1-C_4 alkyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, C_1-C_4 hydroxalkyl, C_1-C_4 alkoxy, carboxy, (C₁-C₄) alkoxy carbonyl, aminocarbonyl, (C₁-C₄) alkyl aminocarbonyl or di(C₁-C₄) alkyl aminocarbonyl radical; and

5 wherein cycloalkyl is a monocyclic or bicyclic carbocyclic alkyl radical of 5-12 ring members, which is optionally partially unsaturated, benzo fused or heterocyclo fused; aryl is a phenyl or biphenyl radical which is optionally benzo fused or heterocyclo fused; heteroaryl is a radical of a monocyclic or bicyclic saturated heterocyclic ring system having 5-8 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally partially unsaturated or benzo-fused and optionally substituted by 1-2 oxo or thioxo radicals; and heteroaryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally benzo-fused or saturated C₃-C₄-carbocyclic-fused.

10 The compound of Claim 4 or a pharmaceutically acceptable salt thereof, wherein

15 R^3 is a radical of the formula



20 25 5. The compound of Claim 4 or a pharmaceutically acceptable salt thereof, wherein

30 wherein

U is C-R¹³ or N;

v and w are each independently C-R¹² or N;

5 R¹¹ and R¹³ are each independently a radical of hydrogen, C₁-C₄ alkyl, halo, trifluoromethyl, cyano, azido, nitro, amidino or R¹⁹-Z¹⁹-; and each R¹¹ is independently a radical of hydrogen, C₁-C₆ alkyl, halo, C₁-C₄ haloalkyl

10 of 1-3 halo radicals, R¹¹-Z¹¹- or R¹¹-Z¹¹-C₁-C₄ alkyl; provided that the combined total number of aryl and heteroaryl radicals in R¹¹, R¹² and R¹³ is 0-1;

wherein each R¹⁹ is independently a hydrogen, C₁-C₄

15 alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted

by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy; and

20 each Z¹⁹ is independently -O-, -S(O)₂-, -CO₂-, -C(O)-, -NR²¹-C(O)-, -NR²¹-NR²¹-;

25 wherein each R³¹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted

30 by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy; and

wherein R⁴ is a radical of hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl, heteroaryl-C₁-C₄ alkyl or 5 each Z³¹ is independently -O-, -NR²¹-, -NR²¹-C(O)-, -C(O)-NR²¹-, -NR²¹-S(O)₂- or -S(O)₂-NR²¹-;

wherein R⁴⁰ is a hydrogen, C₁-C₄ alkyl, aryl, heteroaryl,

10 R²⁰-Z²⁰-C₂-C₄ alkyl radical;

wherein R⁴⁰ is a hydrogen, C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₂ alkyl or heteroaryl-C₁-C₂ alkyl radical; 15 wherein the aryl and heteroaryl radicals of R⁴ and R²⁰ are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, methylthiol, ethylthiol, amino, methylamino, dimethylamino, ethylamino, diethylamino, acetylamino, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy; and

20 R⁵ and R⁶ are each independently a hydrogen, methyl, ethyl, halo, trifluoromethyl, trifluoromethoxy, amino, C₁-C₂ alkylamino, di(C₁-C₂ alkyl)amino, hydroxy, methoxy, or ethoxy radical; and

25 R⁷ is a hydrogen, methyl, ethyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, methoxy or ethoxy radical; and

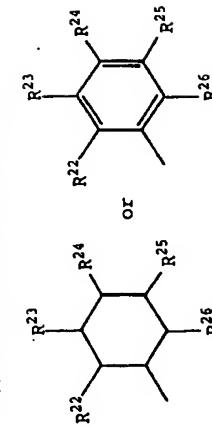
wherein cycloalkyl is a monocyclic or bicyclic carbocyclic alkyl radical of 5-10 ring members, which is optionally partially unsaturated with one double bond, benzo fused or heterocyclo fused; aryl is a phenyl or biphenyl radical which is optionally benzo fused or heterocyclo fused; heterocyclyl is a radical of a monocyclic or bicyclic saturated heterocyclic ring system having 5-8 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms,

233

which is optionally partially unsaturated or benzo-fused and optionally substituted by 1-2 oxo or thioxo radicals; and heteroaryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally benzo-fused or saturated C₃-C₄-carbocyclic-fused.

10 6. The compound of Claim 5 or a pharmaceutically acceptable salt thereof, wherein

R¹ is a radical of the formula



15 wherein

R²², R²³, R²⁴, R²⁵ and R²⁶ are each independently a radical of hydrogen, C₁-C₄ alkyl, halo, trifluoromethyl, cyano, azido, nitro, amidino, R¹⁸-Z¹⁸- or R¹⁸-Z¹⁸-C₁-C₄ alkyl; provided at least one of R²¹, R²², R²³, R²⁴ and R²⁵ is hydrogen; and provided that the combined total number of aryl and heteroaryl radicals in R²², R²³, R²⁴, R²⁵ and R²⁶ is 0-1;

25 wherein each Z¹⁸ is independently -O-, -S-, -S(O)₁-, -CO₂-, -NR²¹-, -NR²¹-C(O)-, -C(O)-NR²¹-, -NR²¹-S(O)₁-, or -S(O)₁-NR²¹-, and

20 7. The compound of Claim 6 or a pharmaceutically acceptable salt thereof, wherein

R¹¹ and R¹³ are each independently a radical of hydrogen, methyl, ethyl, fluoro, chloro, trifluoromethyl, cyano, azido, nitro, amidino, R¹⁹, R¹⁹-O-, R¹⁹-S(O)₂-, R¹⁹-O-C(O)-,

234

wherein aryl is a phenyl or biphenyl radical which is optionally benzo-fused or heterocyclo fused; and heteroaryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally benzo-fused or saturated C₃-C₄-carbocyclic-fused.

10 7. The compound of Claim 6 or a pharmaceutically acceptable salt thereof, wherein

X is NR²;

15 R² is a hydrogen or methyl radical;

R⁴ is a radical of hydrogen, methyl or ethyl radical; and

20 R⁵, R⁶ and R⁷ are each independently a hydrogen radical; and

wherein aryl is a phenyl, biphenyl or naphthyl radical; and heteroaryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms.

30 8. The compound of Claim 7 or a pharmaceutically acceptable salt thereof, wherein

235

236

$R^{19}-C(O)-$, $R^{19}-NR^{21}-C(O)-$ or $R^{19}-NR^{21}-S(O)_2-$; and each R^{12} is independently a radical of hydrogen, methyl, ethyl, fluoro, chloro, trifluoromethyl, trifluoromethoxy,

methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, (methylamino)methyl or (dimethylamino)methyl; provided that the combined total number of aryl and heteroaryl radicals in R^{11} , R^{12} and R^{13} is 0-1; and

wherein each R^{19} is independently a hydrogen, methyl,

ethyl, trifluoromethyl, phenyl, heteroaryl, phenylmethyl or heteroaryl-methyl radical; wherein the phenyl and heteroaryl radicals are optionally substituted by 1-2

radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, fluoro, chloro, methyl, ethyl, trifluoromethyl or trifluoromethoxy.

20

9. The compound of Claim 2 or a pharmaceutically acceptable salt thereof, wherein γ is $-C(O)-NR^{14}R$.

10. The compound of Claim 9 or a pharmaceutically acceptable salt thereof, wherein

X is O or NR^2 ;

11. R^1 is a cycloalkyl, aryl, heterocyclyl or heteroaryl radical which is optionally substituted by 1-4 radicals of C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl of 1-3 halo radicals, cyano, azido, nitro, amidino, $R^{19}-Z^{19}$ or $R^{19}-Z^{19}-C_1-C_4$ alkyl; provided that the total number of aryl and heteroaryl radicals in R^1 is 1-2; and provided R^1 is other than a phenyl or naphthyl having an amino, nitro, cyano, carboxy or alkoxy carbonyl substituent bonded to the ring carbon atom adjacent to the ring carbon atom bonded to $-NR^4-$; and

12. R^1 is a cycloalkyl, aryl, heterocyclyl or heteroaryl radical which is optionally substituted by 1-4 radicals of C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl of 1-3 halo radicals, cyano, azido, amidino, $R^{18}-Z^{18}$ or $R^{19}-Z^{18}$ $-C_1-C_4$ alkyl; provided that the total number of aryl and heteroaryl radicals in R^1 is 0-1; and

heteroaryl, cycloalkyl and heterocyclyl radicals in R^1 is 1-2;

13. R^{10} is independently a hydrogen, C_1-C_4 alkyl, trifluoromethyl, aryl, heteroaryl, aryl- C_1-C_4 alkyl or heteroaryl- C_1-C_4 alkyl radical; wherein the

14. R^{10} is independently a hydrogen, C_1-C_4 alkyl, trifluoromethyl, aryl, heteroaryl, aryl- C_1-C_2 alkyl or heteroaryl- C_1-C_2 alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkylthiol, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, acetylamino, cyano, halo, azido, C_1-C_4 alkyl, trifluoromethyl or trifluoromethoxy; and

15. R^{10} is independently $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-CO_2-$, $-C(O)-$, $-NR^{21}-$, $-NR^{21}-C(O)-$, $-C(O)-NR^{21}-$, $-NR^{21}-S(O)_2-$ or $-S(O)_2-NR^{21}-$; wherein each R^{21} is independently

16. R^1 is a hydrogen or C_1-C_4 alkyl radical;

R^2 is a hydrogen or C_1-C_2 alkyl radical;

17. R^3 is an aryl or heteroaryl radical which is optionally substituted by 1-5 radicals of C_1-C_6 alkyl, halo, C_1-C_4 haloalkyl of 1-3 halo radicals, cyano, azido, nitro,

amidino, $R^{19}-Z^{19}$ or $R^{19}-Z^{19}-C_1-C_4$ alkyl; provided that the total number of aryl and heteroaryl radicals in R^3 is 1-

18. R^3 is other than a phenyl or naphthyl having an amino, nitro, cyano, carboxy or alkoxy carbonyl substituent bonded to the ring carbon atom adjacent to the ring carbon atom bonded to $-NR^4-$; and

19. R^3 is independently a hydrogen, C_1-C_4 alkyl, trifluoromethyl, aryl, heteroaryl, aryl- C_1-C_4 alkyl or heteroaryl- C_1-C_4 alkyl radical; wherein the

237

aryl and heteraryl radicals are optionally substituted by 1-2 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, acetylamino, cyano, halo, C₁-C₄ alkyl, trifluoromethyl or trifluoromethoxy; and

R⁴ is a radical of hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl, heteroaryl-C₁-C₄ alkyl or R²⁰-Z²⁰-C₂-C₄ alkyl radical; and

wherein R²⁰ is a hydrogen, C₁-C₄ alkyl, aryl, heteroaryl, C₁-C₂ alkyl or heteroaryl-C₁-C₂ alkyl radical; wherein the aryl and heteroaryl radicals of R⁴ and R²⁰ are optionally substituted by 1-2 radicals of hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthiol, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, acetylamino, halo, C₁-C₄ alkyl, trifluoromethyl or trifluoromethoxy; and

Z²⁰ is -O- or -NR²¹-; wherein each R²¹ is independently a hydrogen or methyl radical;

R⁵ and R⁶ are each independently a hydrogen, C₁-C₄ alkyl, halo, trifluoromethyl, trifluoromethoxy, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, C₁-C₅ alkanoylamino, hydroxy, C₁-C₄ hydroxymethyl, C₁-C₄ alkoxy, cyano, azido, nitro, carboxy, (C₁-C₄ alkoxy)carbonyl, aminocarbonyl, (C₁-C₄ alkyl)aminocarbonyl or di(C₁-C₄ alkyl)aminocarbonyl radical; and

R⁷ is a hydrogen, C₁-C₄ alkyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, C₁-C₄ hydroxymethyl, C₁-C₄ alkoxy, carboxy, (C₁-C₄ alkoxy)carbonyl, aminocarbonyl,

238

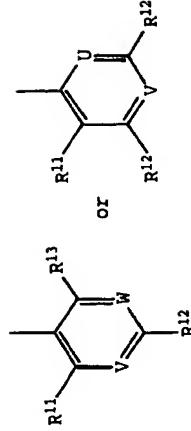
(C₁-C₄ alkyl)aminocarbonyl or di(C₁-C₄ alkyl)aminocarbonyl radical; and

wherein cycloalkyl is a monocyclic or bicyclic carbocyclic alkyl radical of 5-12 ring members, which is optionally partially unsaturated, benzo fused or heterocyclo fused; aryl is a phenyl or biphenyl radical which is optionally benzo fused or heterocyclo fused; heterocyclyl is a radical of a monocyclic or bicyclic system having 5-8 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally partially unsaturated or benzo-fused and optionally substituted by 1-2 oxo or thioxo radicals; and 15 heteroaryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally benzo-fused or saturated C₃-C₄-carbocyclic-fused.

20

11. The compound of Claim 10 or a pharmaceutically acceptable salt thereof, wherein

25 R³ is a radical of the formula



wherein

U is C-R¹³ or N;

30

239

v and w are each independently C-R¹² or N;

R¹¹ and R¹³ are each independently a radical of hydrogen, C₁-C₄ alkyl, halo, trifluoromethyl, cyano, azido, nitro, amidino or R¹⁹-Z¹⁹-; and each R¹² is independently a radical of hydrogen, C₁-C₆ alkyl, halo, C₁-C₄ haloalkyl or 5 halo radicals, R³¹-Z³¹- or R³¹-Z³¹-C₁-C₄ alkyl;

provided that the combined total number of aryl and heteroaryl radicals in R¹¹, R¹² and R¹³ is 0-1; provided 10 when U is C-R¹³ and V and w are each C-R¹², R¹¹ and R¹³ are each other than a nitro, cyano, carboxy or alkoxycarbonyl radical;

wherein each R¹⁹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₄

alkyl or heteroaryl-C₁-C₄ alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted

by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, halo, 20 methyl, ethyl, trifluoromethyl or trifluoromethoxy; and

each Z¹⁹ is independently -O-, -S(O)₂-, -CO₂-, -C(O)-, -NR²¹-C(O)-, -NR²¹-NR²¹-; and

wherein each R²¹ is independently a hydrogen or methyl radical;

25

wherein each R¹¹ is independently a hydrogen, C₁-C₄

alkyl, trifluoromethyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl or heteroaryl-C₁-C₄ alkyl radical; wherein the aryl and heteroaryl radicals are optionally substituted

30 by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy; and

wherein each R¹⁹ is independently a hydrogen, C₁-C₄ alkyl, trifluoromethyl, cyano, azido, nitro, amidino or R¹⁹-Z¹⁹-;

240

each Z³¹ is independently -O-, -NR²¹-, -NR²¹-C(O)-, -C(O)-NR²¹-, -NR²¹-S(O)₂-, or -S(O)₂-NR²¹-;

5 R⁴ is a radical of hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl, heteroaryl-C₁-C₄ alkyl or R²⁰-Z²⁰-C₂-C₄ alkyl radical; and

wherein R²⁰ is a hydrogen, C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₂ alkyl or heteroaryl-C₁-C₂ alkyl radical; 10 wherein the aryl and heteroaryl radicals of R⁴ and R²⁰ are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, methylthiol, ethylthiol, amino, methylamino, dimethylamino, ethylamino, diethylamino, acetylamino, halo, methyl, ethyl, trifluoromethyl or trifluoromethoxy; and

R⁵ and R⁶ are each independently a hydrogen, methyl, ethyl, halo, trifluoromethyl, trifluoromethoxy, amino, C₁-C₂ alkylamino, di(C₁-C₂ alkyl)amino, hydroxy, methoxy or ethoxy radical; and

20 R⁷ is a hydrogen, methyl, ethyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, methoxy or ethoxy radical; and

25

wherein cycloalkyl is a monocyclic or bicyclic carbocyclic alkyl radical of 5-10 ring members, which is

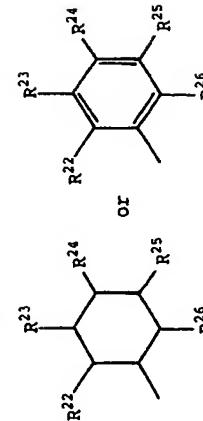
optionally partially unsaturated with one double bond, 30 benzo fused or heterocyclo fused; aryl is a phenyl or biphenyl radical which is optionally benzo fused or heterocyclo fused; heterocyclyl is a radical of a monocyclic or bicyclic saturated heterocyclic ring system having 5-8 ring members per ring, wherein 1-3

241

ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally partially unsaturated or benzo-fused and optionally substituted by 1-2 oxo or thioxo radicals; and heteraryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally benzo-fused or saturated C₃-C₄-carbocyclic-fused.

12. The compound of Claim 11 or a pharmaceutically acceptable salt thereof, wherein

卷之三



wherein

$$\begin{array}{c} | \\ \text{R}^{26} \end{array}$$

$\text{R}^{22}, \text{R}^{23}, \text{R}^{24}, \text{R}^{25}$ and R^{26} are each independently a radical of hydrogen, $\text{C}_1\text{-C}_4$ alkyl, halo, trifluoromethyl, cyano, azido, nitro, amidino, $\text{R}^{18}\text{-Z}^{14}$ or $\text{R}^{18}\text{-Z}^{18}\text{-C}_1\text{-C}_4$ alkyl; provided at least one of $\text{R}^{21}, \text{R}^{22}, \text{R}^{23}, \text{R}^{24}$ and R^{25} is hydrogen; and provided that the combined total number of aryl and heteroaryl radicals in $\text{R}^{22}, \text{R}^{23}, \text{R}^{24}, \text{R}^{25}$ and R^{26}

each Z^{18} is independently $-O-$, $-S-$, $-S(O)_2-$, $-CO_2-$, $-NR^{21}-$, $-NR^{21}-C(O)-$, $-C(O)-NR^{21}-$, $-NR^{21}-S(O)_2-$ or $-S(O)_2-NR^{21}-$

wherein aryl is a phenyl or biphenyl radical which is optionally benzo fused or heterocyclo fused; and heteroaryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms, which is optionally benzo-fused or saturated C₃-C₄-carbocyclic-fused

10 13. The compound of Claim 12 or a pharmaceutically acceptable salt thereof, wherein

x is NR^2 :

15 R^2 is a hydrogen or methyl radical;
 R^4 is a radical of hydrogen, methyl or ethyl radical;
 and
 20 R^5 , R^6 and R^7 are each independently a hydrogen radical;
 and

wherein aryl is a phenyl, biphenyl or naphthyl radical; and heteroaryl is a monocyclic aromatic heterocyclic ring system having 5-6 ring members per ring, wherein 1-3 ring members are oxygen, sulfur or nitrogen heteroatoms.

30 14. The compound of Claim 13 or a pharmaceutically
acceptable salt thereof.

¹¹ R¹ and R¹³ are each independently a radical of hydrogen, methyl, ethyl, fluoro, chloro, trifluoromethyl, cyano, azido, nitro, amidino, R¹⁹-S(O)¹⁹-, R¹⁹-C(O)-, R¹⁹-C(O)R⁵

243
 $R^{19}-C(O)-$, $R^{19}-NR^{21}-C(O)-$ or $R^{19}-NR^{21}-S(O)-$; provided when U is $C-R^{12}$; and V and W are each $C-R^{12}$, R^{11} and R^{13} are each other than a nitro, cyano, carboxy or alkoxycarbonyl radical; and provided that the combined total number of 5
 5 aryl and heteroaryl radicals in R^{11} and R^{13} is 0-1;

each R^{12} is independently a radical of hydrogen, methyl, ethyl, fluoro, chloro, trifluoromethyl,

trifluoromethoxy, methoxy, ethoxy, amino, methylamino, 10
 dimethylamino, acetylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl,

(methylamino)methyl or (dimethylamino)methyl; and 15
 wherein each R^{19} is independently a hydrogen, methyl, ethyl, trifluoromethyl, phenyl, heteroaryl, phenylmethyl or heteroaryl-methyl radical; wherein the phenyl and heteroaryl radicals are optionally substituted by 1-2 radicals of hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, acetylamino, cyano, fluoro, 20
 chloro, methyl, ethyl, trifluoromethyl or trifluoromethoxy.

15. The compound of Claim 1 which is:

25
 2-cyclohexyloxy-5-(2-chlorophenylcarbonylamino)pyridine; 2-cyclohexyloxy-5-(2-methylphenylcarbonylamino)pyridine; 2-cyclohexyloxy-5-(2,6-dichlorophenylcarbonylamino)pyridine; 30
 2-cyclohexyloxy-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-cyclohexyloxy-5-(2,6-dimethylphenylcarbonylamino)pyridine; 35
 2-(2,4-dimethylphenoxy)-5-(2-chlorophenylcarbonylamino)pyridine; 2-(2,4-dimethylphenoxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine;

2-(2,4-dimethylphenoxy)-5-(2-methylphenylcarbonylamino)pyridine; 2-(2,6-dimethyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(2-methylphenylcarbonylamino)pyridine; 2-(2-methylphenylcarbonylamino)pyridine; 5
 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine; 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 10
 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 15
 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(2-methyl-4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 20
 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 25
 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 30
 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 2-(4-chlorophenoxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine; 35
 2-(1-naphthylloxy)-5-(2-methylphenylcarbonylamino)pyridine; 2-(1-naphthylloxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine;

245

2-(1-naphthyl oxy)-5-(2,6-dimethylphenylcarbonylamino)pyridine;
2-(2-methyl-3-pyridyl oxy)-5-(2,6-dichlorophenylcarbonylamino)pyridine;
5 2-(2-methyl-4-chlorophenoxy)-5-(13,5-dimethyl-4-isoxazolyl)carbonylamino)pyridine;
2-(2-methyl-4-chlorophenoxythiol)-5-(2,6-dimethylphenylcarbonyl amino)pyridine;
10 2-cyclohexylaminino-5-(2,6-dichlorophenylcarbonylamino)pyridine;
2-cyclohexylaminino-5-(2,6-dimethylphenylcarbonylamino)pyridine;

15 2-(2-methylcyclohexylaminino)-5-(2,6-dichlorophenylcarbonyl amino)pyridine;
2-(2-methylcyclohexylaminino)-5-(2-methylphenylcarbonyl amino)pyridine;
2-(2,4-dimethylphenylaminino)-5-(2-fluorophenylcarbonyl amino)pyridine;
20 2-(2,4-dimethylphenylaminino)-5-(2-chlorophenylcarbonyl amino)pyridine;
2-(2,4-dimethylphenylaminino)-5-(2,6-dichlorophenylcarbonyl amino)pyridine;

25 2-(2,4-dimethylphenylaminino)-5-(2,6-dichlorophenylcarbonyl amino)pyridine;
2-(2-methylphenylaminino)-5-(2-methylphenylcarbonyl amino)pyridine;
30 2-(2-methylphenylaminino)-5-(2-methylphenylcarbonyl amino)pyridine;
2-(2-methylphenylaminino)-5-(2,6-dichlorophenylcarbonyl amino)pyridine;
35 2-(2,4-dimethylphenylaminino)-5-(2,6-dimethylphenylaminino)pyridine;

246

2-(2-methyl-4-chlorophenoxyamino)-5-(2-methylphenylcarbonylamino)pyridine;
2-(2-methyl-4-chlorophenoxyamino)-5-(2,6-dimethylphenylcarbonylamino)pyridine; or
5 2-(2-methyl-4-chlorophenoxyamino)-5-(2-methylphenylaminocarbonyl)pyridine.

16 A pharmaceutical composition comprising a compound
10 of Claim 1 and a pharmaceutically acceptable carrier.

17 A method for prophylaxis or treatment of
15 inflammation comprising administering an effective
amount of a compound of Claim 1.

18 A method for prophylaxis or treatment of
20 inflammation comprising administering an effective
amount of a composition of Claim 16.

19 A method of treating cancer which comprises
25 administering an effective amount of a compound of Claim
1.

20 A method of treating cancer which comprises
25 administering an effective amount of a composition of
Claim 16.

30

21 A method for prophylaxis or treatment of rheumatoid
arthritis, Pagets disease, osteophorosis, multiple
myeloma, uveitis, acute or chronic myelogenous
35 leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome

248

(ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone

resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain

trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due

to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound of Claim 1.

5 resorption diseases, graft vs. host reaction,

Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain

trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due

to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound of Claim 1.

5

23. A method for prophylaxis or treatment of pain comprising administering an effective amount of a compound of Claim 1.

5

24. A method for prophylaxis or treatment of pain comprising administering an effective amount of a compound of Claim 16.

15 22. A method for prophylaxis or treatment of rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis,

20 rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's

25 syndrome, type I diabetes, type II diabetes, cancer, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain

trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due

30 to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound of Claim 16.

THIS PAGE BLANK (USPTO)

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)